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## ORIGINAL ARTICLES

# STUDIES WITH TULAREMIA VACCINES IN VOLUNTEERS*

### III. SEROLOGIC ASPECTS FOLLOWING INTRACUTANEOUS OR RESPIRATORY CHALLENGE IN BOTH VACCINATED AND NONVACCINATED VOLUNTEERS

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Previous reports from this laboratory have described the clinical aspects of tularemia infection in both vaccinated and nonvaccinated volunteers following intracutaneous[4] and respiratory[5] challenge. These studies offered an excellent opportunity to compare the serial antibody responses following vaccination with killed or viable attenuated vaccine as well as the serologic picture in nonvaccinated and vaccinated volunteers challenged by either the cutaneous or respiratory route. It is the purpose of this report to describe the serologic aspects of experimental tularemia in man.

**Materials and Methods.** Foshay killed (phenolized) vaccine and the viable attenuated vaccine were administered as previously described (Saslaw *et al.*[4,5]). Challenge with *P. tularensis* (Schu S4 strain) by both the cutaneous[4] and respiratory[5] route in both nonvaccinated and vaccinated volunteers has also been described.

SERUM. Blood was collected in sterile tubes from volunteers at weekly intervals following vaccination and at biweekly intervals after challenge. Serum obtained from these specimens was stored at −20° C.

BACTERIAL AGGLUTINATION TEST. To each 0.5 ml. of serum dilutions, 0.5 ml. of formalin-killed bacterial suspension (approximately $3 \times 10^9$ organisms) was added, and the tests incubated overnight in a 37° C. water bath before reading. Titers were recorded as the highest dilution showing at least 2+ agglutination.

HEMAGGLUTINATION TEST. These tests were performed as described by Alexander, Wright and Baldwin[1] and Wright and Feinberg[6]. In brief, washed human type "O" red blood cells were sensitized by incubation with *P. tularensis* polysaccharide†, washed and then 0.5 ml. added to 0.5 ml. of serum dilutions.

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†Kindly supplied by Dr. P. S. Nicholes, Utah University.

The tubes were incubated for 2 hours at room temperature and then read. The titer was recorded as the greatest dilution of serum giving partial or complete hemagglutination.

**Results.** SEROLOGIC RESPONSE AFTER VACCINATION. *Bacterial Agglutinations.* As can be seen in Fig. 1, an earlier rise to peak titers was observed in the 27 volunteers receiving killed vaccine; peak titers varying from 1:40 to 1:2560 (mean titer, 1:320) were obtained 7 to 16 days postvaccination. After viable vaccine in the 29 subjects studied, a slower progressive rise with slightly higher peak titers 1:80 to 1:2560 (mean titer, 1:640) was observed 23 to 59 days postvaccination. However, a gradual but more rapid decline from peak titers was observed in the killed vaccine group while there was a tendency to plateau in titers following living vaccine. Thus at 12 weeks (Fig. 1), titers after killed vaccine varied from 0 to 1:640 with a mean of 1:80 as compared to a range of 1:40 to 1:2560 with a mean of 1:640 after living vaccine. Subsequent periods of comparison of vaccine effect alone were limited by subsequent challenge of volunteers. However, in the killed vaccine group, there were 9 volunteers where follow-up was possible as late as 17 to 50 weeks while in the viable vaccine group 15 volunteers were followed for 15 to 22 weeks. At the 15 to 17 week and 20 to 22 week intervals, the comparative titers in both groups were essentially the same as that observed at 12 weeks (Fig. 1).

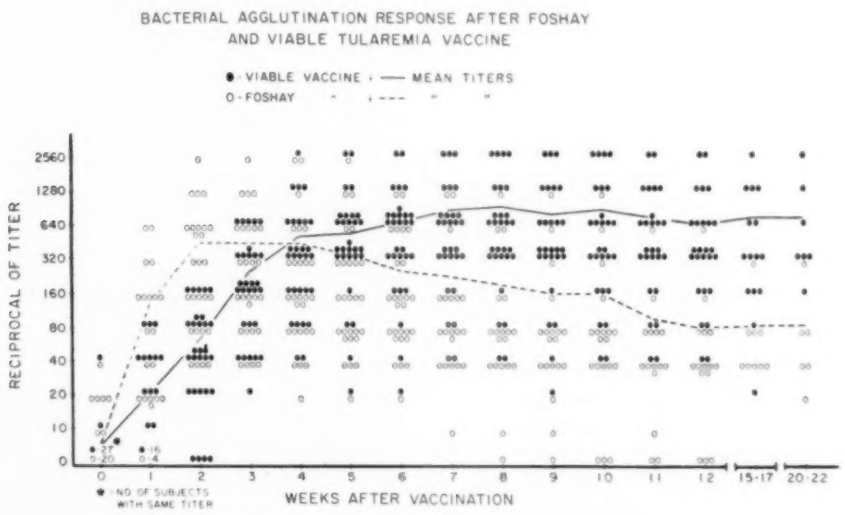


Fig. 1

*Hemagglutination Results.* As can be seen in Fig. 2, the hemagglutination titer curves in both vaccine groups paralleled those observed in bacterial agglutination (Fig. 1). After 20 to 22 weeks, mean titers after killed vaccine were 1:320 as compared to 1:10,240 after viable vaccine. One other interesting difference in serologic results was noted between the vaccine groups. Following vaccination with killed vaccine, both the bacterial and hemagglutination titers were significantly elevated between 1 to 2 weeks later. However, after viable vaccine, the hemag-

glutination titers showed earlier significant 4-fold or greater rise in titers as compared to bacterial agglutination results. For example, after 1 week, 20 of 29 hemagglutination titers as compared to 12 of 29 bacterial agglutination titers were elevated; after 2 weeks, all of 29 hemagglutination and 23 of 29 bacterial agglutination titers were significantly raised. After 3 weeks, the bacterial agglutination titers were all significantly increased.

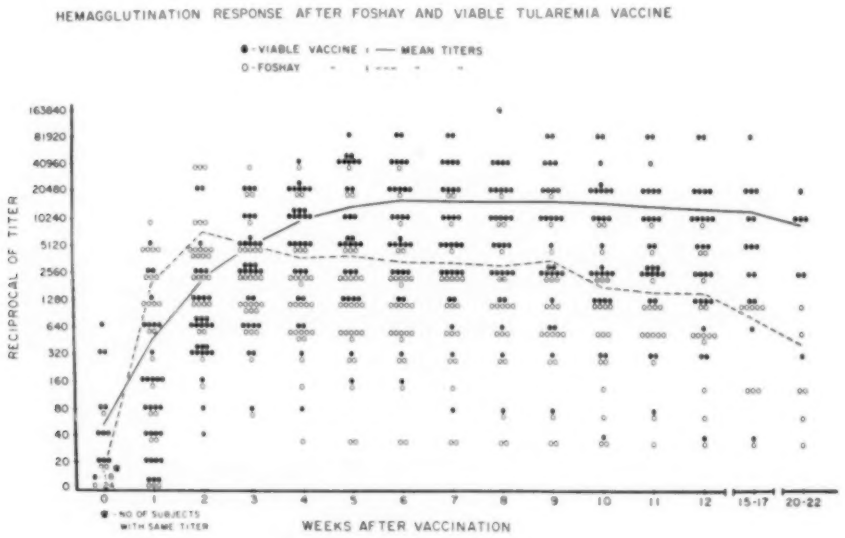


Fig. 2

SEROLOGIC RESPONSE AFTER INTRACUTANEOUS CHALLENGE IN NONVACCINATED VOLUNTEERS. As can be seen in Fig. 3, both bacterial and hemagglutination titer curves in 12 volunteers challenged with approximately 10 organisms resembled the response observed after vaccination with viable attenuated vaccine (Figs. 1 and 2), except that peak titers in both tests were observed between 3 to 5 weeks postchallenge as compared to 6 to 8 weeks with viable vaccine and 1 to 2 weeks after killed vaccine. Significant changes in titer were first observed in the hemagglutination test between 11 to 21 days (average 14 days) and peak titers from 1:2,560 to 1:163,840 (mean 1:20,480) after 21 to 39 days (average 27.5). Bacterial agglutination titers were first significantly elevated 17 to 25 days (average 21 days) after challenge; peak titers of 1:20 to 1:2,560 (mean 1:320) were observed 23 to 36 days (average 29 days) after challenge. After 12 weeks, there was relatively little change in titers as noted with viable vaccine.

SEROLOGIC RESPONSE AFTER INTRACUTANEOUS CHALLENGE IN VOLUNTEERS PREVIOUSLY RECEIVING KILLED VACCINE. As can be seen in Fig. 4, base-line bacterial agglutination titers in 19 volunteers following vaccination and prior to challenge varied from 1:20 to 1:640. Twelve of the 19 volunteers showed significant 4-fold or greater increase in titers following challenge. Although all 19 of these men showed local lesions, only 6 (Nos. 13, 14, 16, 20, 27, 29) showed systemic evidence of infection

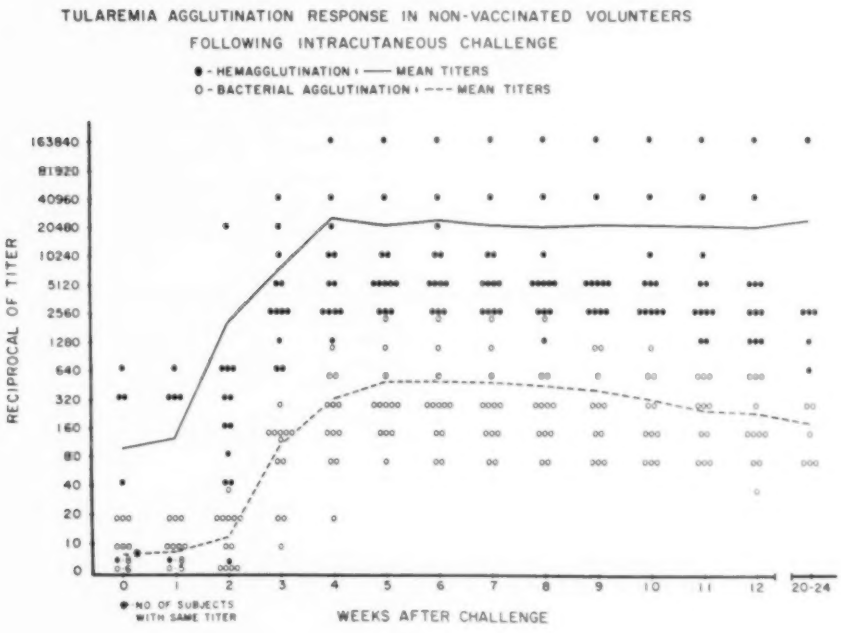
TULAREMIA AGGLUTINATION RESPONSE IN NON-VACCINATED VOLUNTEERS
FOLLOWING INTRACUTANEOUS CHALLENGE
● - HEMAGGLUTINATION ; —— MEAN TITERS
O - BACTERIAL AGGLUTINATION ; --- MEAN TITERS
RECIPROCAL OF TITER
163840
81920
40960
20480
10240
5120
2560
1280
640
320
160
80
40
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 20-24
● NO. OF SUBJECTS WITH SAME TITER
WEEKS AFTER CHALLENGE

Fig. 3

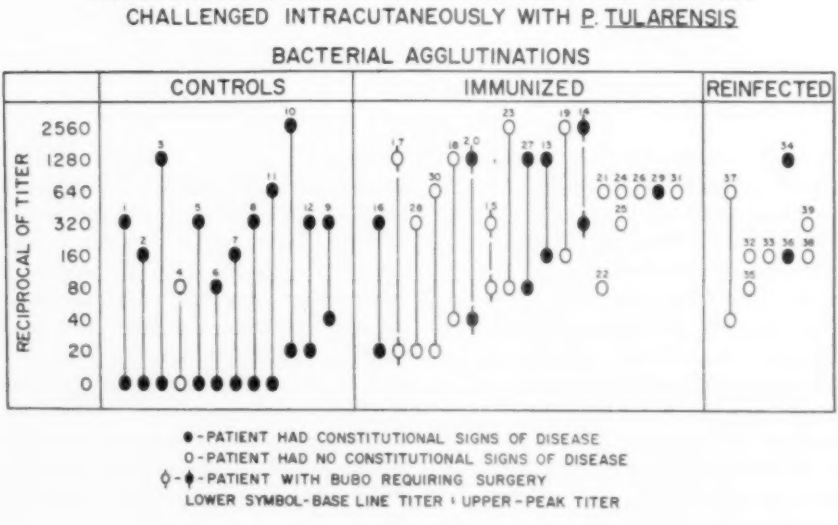
AGGLUTININ RESPONSE IN FOSHAY-IMMUNIZED AND CONTROLS
CHALLENGED INTRACUTANEOUSLY WITH P. TULARENSIS
BACTERIAL AGGLUTINATIONS
CONTROLS
IMMUNIZED
REINFECTED
RECIPROCAL OF TITER
2560
1280
640
320
160
80
40
20
0
● - PATIENT HAD CONSTITUTIONAL SIGNS OF DISEASE
O - PATIENT HAD NO CONSTITUTIONAL SIGNS OF DISEASE
◊ - ♦ - PATIENT WITH BUBO REQUIRING SURGERY
LOWER SYMBOL - BASE LINE TITER ; UPPER - PEAK TITER

Fig. 4

(Saslaw *et al.*[4]); one of these (No. 29) showed no change in antibody titer. There apparently was no correlation between prechallenge titer and the appearance of systemic disease. As can be seen in Fig. 4, 1 (No. 16) of 4 with prechallenge titers of 1:20 became ill. One (No. 20) of 2 and 1 (No. 27) of 4 with prechallenge titers of 1:40 and 1:80, respectively, showed systemic

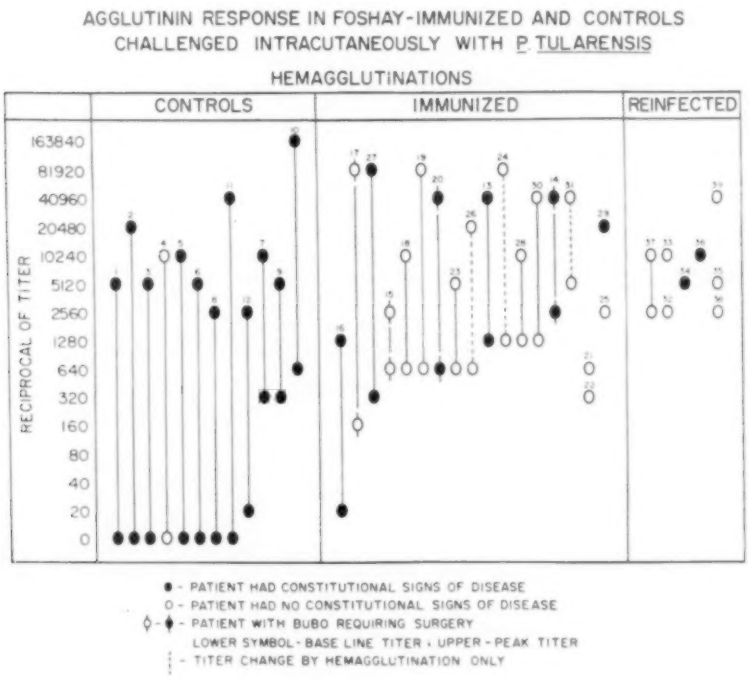


Fig. 5

evidence of infection as did 1 (No. 13) of 2, 1 (No. 14) of 2, and 1 (No. 29) of 5 with preinoculation titers of 1:160, 1:320, and 1:640, respectively.

A similar situation was observed in terms of the hemagglutination response (Fig. 5) with the exception that 3 volunteers (Nos. 24, 26, 31) showed significant 4-fold or greater antibody responses by hemagglutination but not by bacterial agglutination tests. Thus 15 of 19 showed significant antibody changes by hemagglutination as compared to 12 of 19 in the bacterial agglutination test. Again, as with bacterial agglutination, there was no correlation between preinoculation titer and subsequent systemic disease (Fig. 5). The hemagglutination titers first showed significant increases after challenge between 16 to 31 days (average 24.5 days) as compared to 26 to 35 days (average 30 days) with bacterial agglutination titers. Peak hemagglutination titers were observed between 27 to 38 days (average 31.3 days) as compared to 31 to 48 days (average 39 days) with bacterial agglutinations.

SEROLOGIC RESPONSE AFTER REINFECTION BY INTRACUTANEOUS CHALLENGE. As previously described (Saslaw *et al.*[4]) 8 volunteers who had previously

been infected as controls were rechallenged 2 to 8 months later. Local lesions were observed in all again, and systemic evidence of infection in 2 (Nos. 34, 36). As can be seen in Figs. 4 and 5, change in titer was observed in 1 (No. 37) who showed no systemic evidence of infection. No serologic alterations were observed in the other 7 volunteers and again base-line titers with a mean titer of 1:5,120 between 14 to 38 days (average 26 days). Significant rises in bacterial agglutination titers were observed between the 14th to 31st days (average 20 days); peak titers varying from 1:40 to 1:2,560 with a mean titer of 1:640 were observed between the 14th to 41st days (average 30 days) and plateaued so that similar titers were still present at 24 weeks.

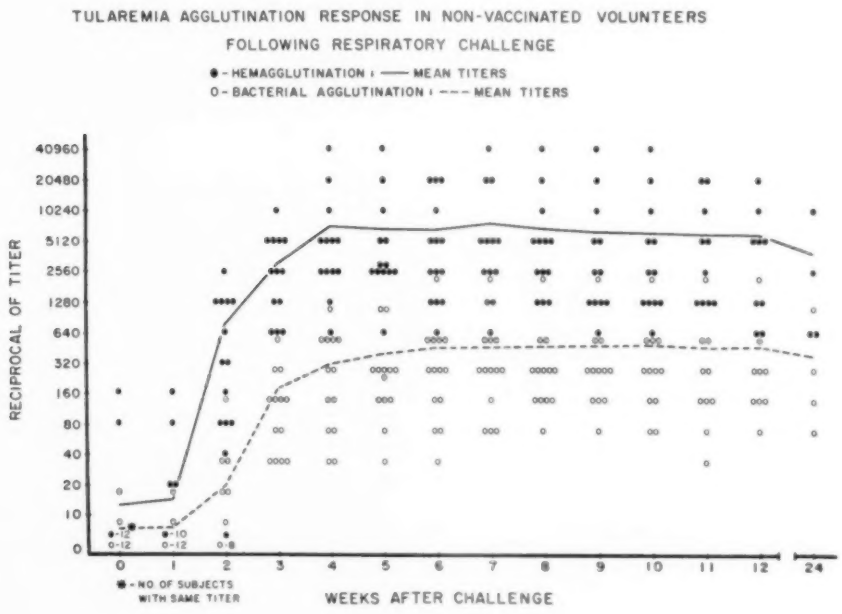


Fig. 6

did not appear to correlate with the clinical outcome.

SEROLOGIC RESPONSE IN NONVACCINATED VOLUNTEERS FOLLOWING RESPIRATORY CHALLENGE. The antibody response following respiratory challenge with 10 to 50 *P. tularensis* organisms in 14 nonvaccinated volunteers infected by this route (Saslaw *et al.*[5]) is shown in Fig. 6. The hemagglutination titers first showed significant titer rises between 10 to 21 days (average 15 days) and peak titers from 1:640 to 1:40,960

RESPONSE IN VOLUNTEERS CHALLENGED BY THE RESPIRATORY ROUTE AFTER VACCINATION WITH KILLED VACCINE. As previously described (Saslaw *et al.*[5]), 8 of 14 volunteers who received killed Foshay vaccine showed systemic evidence of infection after challenge. As can be seen in Fig. 7, only 2 (Nos. 11, 19) showed 4-fold rises in both the bacterial agglutination (32 and 34 days) and hemagglutination titers (Fig. 8) (20 and 22 days); a 3rd volunteer (No. 9) showed a significant

AGGLUTININ RESPONSE IN FOSHAY-IMMUNIZED AND CONTROLS CHALLENGED BY THE RESPIRATORY ROUTE WITH P. TULARENSIS

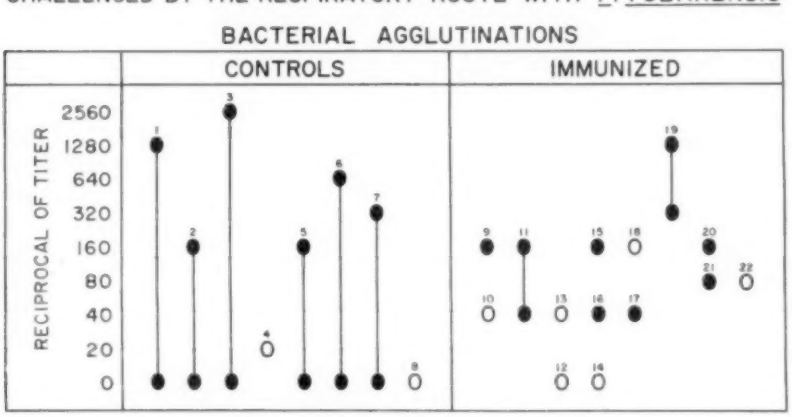


Fig. 7

AGGLUTININ RESPONSE IN FOSHAY-IMMUNIZED AND CONTROLS CHALLENGED BY THE RESPIRATORY ROUTE WITH P. TULARENSIS

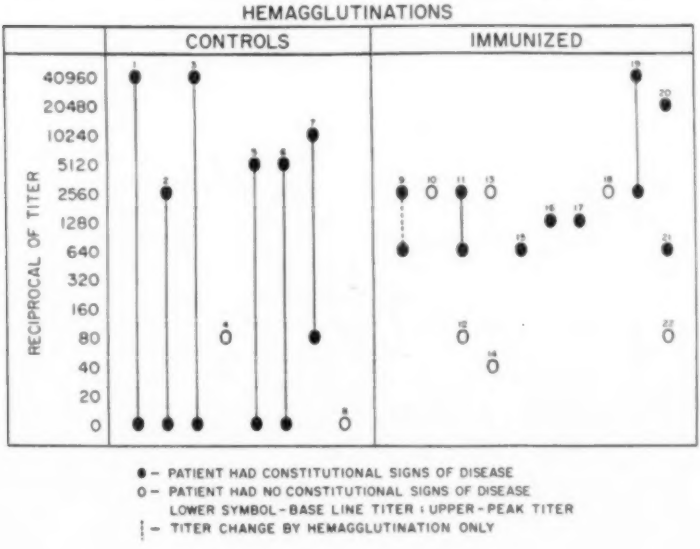


Fig. 8

AGGLUTININ RESPONSE IN VIABLE VACCINE-IMMUNIZED AND CONTROLS CHALLENGED BY THE RESPIRATORY ROUTE WITH P. TULARENSIS

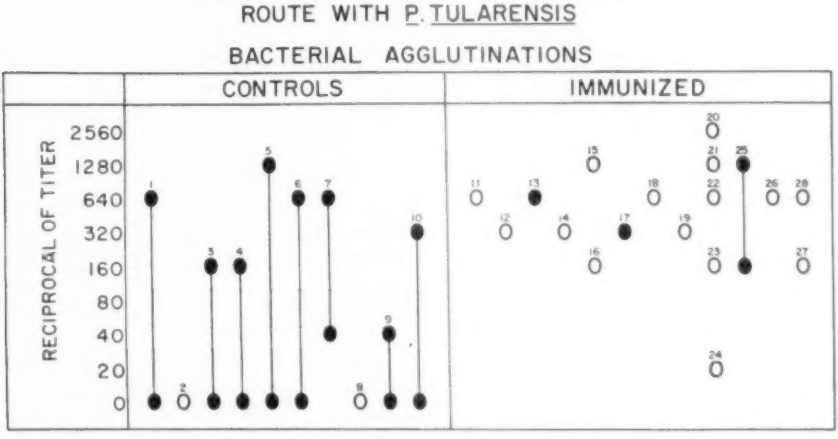


Fig. 9

AGGLUTININ RESPONSE IN VIABLE VACCINE-IMMUNIZED AND CONTROLS CHALLENGED BY THE RESPIRATORY ROUTE WITH P. TULARENSIS

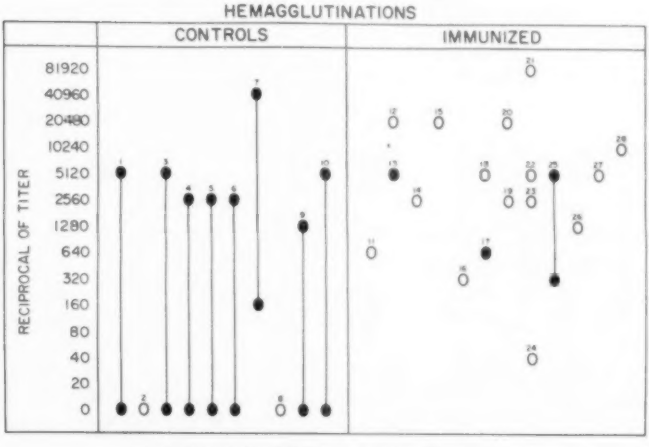


Fig. 10

rise after 22 days in the latter test, only. Again as can be seen in Figs. 7 and 8, there was no correlation of prechallenge titers to resistance.

RESPONSE IN VOLUNTEERS CHALLENGED BY THE RESPIRATORY ROUTE AFTER VACCINATION WITH VIABLE VACCINE. As previously described[5], only 3 of 18 volunteers receiving viable vaccine showed systemic evidence of infection after respiratory challenge. As can be seen in Fig. 9, only 1 (No. 25) showed a significant rise in the bacterial agglutination test by the 27th day and in the hemagglutination test (Fig. 10) by the 20th day, postchallenge.

**Discussion.** These studies of experimental tularemia infection by either intracutaneous[4] or respiratory[5] routes have afforded a unique opportunity for a controlled serologic evaluation. By knowing the exact time and route of infection, the subsequent serial antibody results could be compared critically to known base-lines in both vaccinated and nonvaccinated volunteers.

These studies have demonstrated that a significant rise in antibody titer by either bacterial agglutination or hemagglutination tests was observed earlier following administration of killed vaccine as compared to living vaccine. However, peak titers were more sustained following the latter. Following immunization with viable vaccine or challenge with *P. tularensis* by either the intracutaneous or respiratory routes, the hemagglutination test usually showed significant 4-fold or greater titer increases about 1 week before the bacterial agglutination test. A similar sequence was observed after challenge in volunteers previously vaccinated with either killed or viable vaccine. This sequence has also been noted in laboratory-acquired infections (Charkes[2]). In 4 instances, it was also found that the significant antibody rise was observed only with the hemagglutination test following challenge in vaccinated individuals.

Following intracutaneous challenge in nonvaccinated controls who were treated promptly when systemic manifestations appeared, serologic confirmation of infection by both bacterial and hemagglutination tests was obtained (Fig. 4). However, although local lesions after intracutaneous challenge were observed in all individuals previously vaccinated with killed vaccine, serologic evidence of infection was not obtained in 7 of 19 in the bacterial agglutination test (Fig. 4) and 4 of 19 in the hemagglutination test (Fig. 5). One volunteer (No. 29) who showed constitutional signs of disease reacted in neither test.

Following respiratory challenge in nonvaccinated controls, all of 14 showing clinical evidence of infection showed significant antibody rises in both serologic tests employed (Figs. 7, 8, 9 and 10). However, in the group receiving Foshay killed vaccine, only 2 of 8 (Fig. 8) showing systemic evidence of infection showed significant bacterial and hemagglutination titer rises, while a 3rd volunteer showed a change in the latter test only (Fig. 9). Similarly after viable vaccine, respiratory challenge resulted in significant serologic changes in both tests in only 1 of 3 showing systemic evidence of infection (Figs. 9, 10).

With the intracutaneous route of challenge, there could be no doubt as to whether or not infection was established since the cutaneous lesion was an indicator as to whether or not there was a "take." However, one could not predict from either the bacterial or hemagglutination prechallenge titer as to whether systemic evidence of infection could be anticipated. For example, 1 of 4 with bacterial agglutination baseline titer of only 1:20 became ill while 1 of 5 at the highest prechallenge titer

of 1:640 also became ill. Between these 1 of 2, 1 of 4, 1 of 2 and 1 of 2, respectively, showed systemic disease after prechallenge titers of 1:40, 1:80, 1:160, and 1:320, respectively. Similarly infection was produced in 1 of 1 each with a hemagglutination titer of 1:20,448 and 1:20, respectively. Volunteers with intermediate prechallenge titers of 1:160, 1:320, 1:640, 1:1280, 1:2560 and 1:5,120 had infections in 0 of 1, 1 of 2, 1 of 7, 1 of 4, 1 of 2, and 0 of 1, respectively.

Similarly the prechallenge titers in volunteers receiving respiratory challenge did not correlate with clinical evidence of infection. In this group the relationship would be more difficult to evaluate since there were obviously "no takes" as exemplified by lack of clinical disease in both controls and vaccinated men challenged simultaneously.

It is conceivable that early, prompt, specific therapy prevented the development of serologic evidence particularly in the respiratory challenge group who had been previously vaccinated with either killed or viable vaccine. Similarly, reinfection by intracutaneous inoculation resulted in serologic alterations in only 1 of 8 volunteers. Thus in the vaccinated or reinfected group, early therapy may have contributed in part to the lack of antibody response although 2 cases of untreated reinfection laboratory-acquired tularemia (Green and Eigelsbach[3]) showed no changes in humoral antibody titer.

The clinical diagnosis of tularemia could easily be made following intracutaneous challenge (Saslaw *et al.*[4]). However, as noted previously[5], volunteers infected via the respiratory route showed a grippal-symptom complex that would tax one's clinical acumen. Since blood cultures were consistently negative following both routes of challenge, they offered no help. Pharyngeal cultures were only rarely positive under the conditions of this study[5]. Thus the bacterial and hemagglutination tests during the first week of infection was of little help in nonvaccinated volunteers when the problem of recognition would be most desirable. The hemagglutination test showed significant alteration between 10 to 21 days and bacterial agglutination between 14 to 31 days.

In the vaccinated volunteers showing serologic evidence of infection after respiratory challenge, hemagglutinins were not helpful until after 20 to 22 days and bacterial agglutinins after 27 to 34 days.

Although under the conditions of this study, prompt therapy with streptomycin or tetracycline could mask the serologic evidence of infection with *P. tularensis*, it is also conceivable that early empirical treatment of an undiagnosed tularemic infection with a broad-spectrum antibiotic under field conditions could similarly impair the serologic response.

**Summary.** Serial bacterial and polysaccharide hemagglutination antibody titers were compared in volunteers vaccinated with phenolized or viable attenuated tularemia vaccines. Similar studies were conducted in both vaccinated and nonvaccinated volunteers following challenge with *P. tularensis* by either the intracutaneous or respiratory routes.

1. Peak titers in both serologic tests appeared later after viable vaccine than with killed vaccine but were more sustained.

2. Following vaccination with viable vaccine or challenge with virulent *P. tularensis* by either the intracutaneous or respiratory route, hemagglutination tests showed significant titer increases about 1 week before bacterial agglutination tests.

3. In nonvaccinated volunteers, hemagglutinins were significantly elevated 10 to 21 days postchallenge by either respiratory or intracutaneous route and bacterial agglutinins after 14 to 31 days.

4. In vaccinated volunteers, the antibody changes which were observed infrequently following respiratory challenge also showed earlier hemagglutination responses (20 to 22 days) as compared to bacterial agglutinations (27 to 34 days).

5. Prechallenge titers by either test did not correlate with the incidence of systemic infection.

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## SUMMARIO IN INTERLINGUA

### Studios con Vaccinos Contra Tularemia in Voluntarios III. Aspectos Serologic post Provocation Intracutanee o Respiratori in Voluntarios Vaccinate e Non Vaccinate

Determinationes serial del titros de anticorpore bacterial e hemagglutinatori polysaccharidic esseva comparate in voluntarios vaccinate con vaccinos de tularemia phenolisate o viabile e attenuate. Simile studios esseva executate in vaccinate e etiam in non-vaccinate voluntarios post provocation con *Pasteurella tularensis* per via intracutanee o per via respiratori.

1. In ambe le tests serologic, le titros maximal occurreva plus tarde post vaccino viabile que post vaccino phenolisate, sed post vaccino viabile le titros esseva plus perdurative.

2. Post vaccination con vaccino viable o post provocation con virulente *P. tularensis* per via intracutanee o per via respiratori, le tests de hemagglutination monstrava significative augmentos de titro circa un septimana plus tosto que le tests de agglutination bacterial.

3. In non-vaccinate voluntarios, le hemagglutininas esseva significativemente elevate 10 a 21 dies post le provocation per via respiratori o per via intracutanee. Le mesmo valeva pro le agglutininas bacterial post 14 a 31 dies.

4. In vaccinate voluntarios, le infrequentemente observate alterationes de anticorpore post provocation respiratori esseva etiam characterisate per plus prompte responsas hemagglutinatori (20 a 22 dies) in comparation con le agglutination bacterial (27 a 34 dies).

5. Le titros ante le provocation, secundo ambe tests, non esseva correlationate con le incidentia de infection systemic.

# A STUDY OF THE MECHANISM BY WHICH QUINACRINE INHIBITS L.E. CELL FORMATION*

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Although several antimalarial drugs have been shown to have a suppressive action on rheumatoid arthritis (Cohen and Calkins[1], Pomeroy *et al.*[10]) and systemic lupus erythematosus (Dubois[2], Page[9]), their mode of action is unknown and no explanation has been found for the curious fact that a series of drugs acting against malaria should also be effective against the totally unrelated connective tissue diseases. Furthermore, these drugs have the interesting property of inhibiting L.E. cell formation. Theoretically, it seems that an understanding of the mechanism by which antimalarials block L.E. cell formation *in vitro* might furnish a clue to their *in vivo* antirheumatic action. If so, blocking of L.E. cell formation might serve as a screening device by which the more promising of the 14,000 antimalarials which have already been synthesized might be selected for clinical trial. These considerations justify a further attempt to elucidate the mechanism whereby antimalarials block L.E. cell formation.

THE PRESENT SITUATION IN PERSPECTIVE. Production of L.E. cells is the end result of a chain of events into which numerous factors enter. Our present knowledge concerning this subject has been well summarized by Holman[5], but, for our immediate purposes, it will only be necessary to keep in mind a few of the well established features of the process, such as the following: 1) The serum of many (but not all) patients with active systemic lupus erythematosus contains a series of abnormal globulins, some of which are capable of reacting with the nuclear material of old, damaged or dead leukocytes. Apparently, healthy cytoplasm with an intact outer membrane is impervious to attack by these factors. Anticytoplasmic factors, specific anti-DNA and antihistone factors also exist but apparently are not concerned in L.E. cell production. 2) The L.E. serum factor, after traversing the cell membrane and cytoplasm, can react with nuclear material in a few seconds to cause a rise in its protein content and an alteration in its staining properties (Rifkind and Godman[11]). The altered nucleus is then extruded from the cell to become an L.E. body. 3) Such L.E. bodies are subsequently phagocytosed by the remaining viable leukocytes to form the characteristic L.E. cell.

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†NIAMD GRANT, Number 2A-5145(C2).

In patients taking 300 mg. of quinacrine by mouth daily, Shannon *et al.*[12] found plasma concentrations of 64 to 103 μg. per L. Eighty to 90% of the plasma quinacrine was bound to nondiffusible plasma constituents, "presumably plasma albumin." Erythrocytes contained one to two times as much, and leukocytes in excess of 200 times that of the plasma concentrations. *In vitro*, quinacrine progressively diffused from leukocytes into the surrounding plasma so that it is not, apparently, irreversibly bound to the leukocytes.

If quinacrine is added, in concentrations of 0.4 mg. per ml., or more, to fresh blood which on incubation shows many L.E. cells, no L.E. cells will then be found by standard laboratory techniques. This striking inhibition of L.E. cell production, which we have confirmed many times, could, theoretically, be due to action at any one or more of the following three points in the chain of events which lead to L.E. cell formation: First, quinacrine could act on the serum factor so as to render it inert, an explanation favored by Dubois[3]. Second, it could react with the nuclear material in such a way as to protect it from reacting with the L.E. serum factor. This view was favored by Kurnick[6], who believed that it combined with nuclear DNA to protect it from L.E. serum factor, thus preventing L.E. body formation. Lee[7], studying the spontaneous disruption and agglutination of dying leukocytes found that the clump was held together by a network of nuclear material. In the presence of L.E. serum factor the nuclear material was altered so that it no longer held the clump together. This reaction was favored rather than inhibited by quinacrine in concentrations of 0.25 mg. per ml. Thus, in this experimental situation, quinacrine apparently did not protect the nuclear material from interaction with L.E. serum factor. Lastly, quinacrine could prevent L.E. cell formation by arresting phagocytosis by the remaining live leukocytes. Lee[7] recognized this possibility, but Dubois[3] believed that he had excluded it because he found inhibition in the presence of leukocytes which could still ingest carbon particles and staphylococci. These conflicting views seem to justify further study of the process.

In the studies reported below we used quinacrine hydrochloride (Atabrine) because most of the previous work in this field has been done with it and because it fluoresces in ultraviolet light and so can be identified both in cells and in serum.

**Experimental Procedures and Results.** In the experiments reported below, quinacrine was obtained from a stock solution 10 mg. per ml. in strength and with an average pH of 4.5. Several checks were made with the solution buffered with Imidazole to pH 7.4 but there was no apparent difference in results. The first three experiments were planned to be exploratory in nature.

1. ELECTROPHORESIS OF QUINACRINE AND L.E. SERUM. Using a Spinco, model R, series D, Durrum apparatus for electrophoresis with S & S, 2043A paper, a barbiturate buffer system (Spinco Buffer B-2) and a current of 2.5 milliamperes, a quinacrine-serum mixture was placed on center and observed from 16 to 24 hours thereafter. The mixture was prepared by incubating at 37° C. for 6 hours L.E. serum to which quinacrine had been added to make a concentration of 0.1 mg. per ml.

When examined under ultraviolet light, the greater part of the quinacrine was found, by fluorescence, to occupy the same zone as the gamma globulins although there appeared to be a slight retrograde migration to-

wards the cathode. No conclusions could, however, be drawn because neither globulins nor quinacrine had moved sufficiently from the point of application. Identical serum-quinacrine mixtures were, therefore, placed at 9 and 12 cm. from center toward the cathode, and, under these conditions of increased "wetness," the quinacrine moved toward the cathode and the serum globulins toward the anode so that they were quite clearly separated into adjacent areas. Therefore if any binding of quinacrine to the gamma globulins occurred, the amount of quinacrine involved was too little to be detected by ultraviolet fluorescence.

2. LOCATION OF QUINACRINE IN LEUKOCYTES AND L.E. CELLS. Quinacrine was added to normal blood, without anticoagulant, in serial concentrations from 0.1 mg. per ml. through 1.0 mg. per ml., smeared and examined by ultraviolet light. It was found to be mainly concentrated in the cytoplasm of the leukocytes, the nuclei fluorescing feebly by comparison, and erythrocytes not at all. The greater affinity of quinacrine for cytoplasm may point to cytoplasmic interaction as a factor in L.E. cell inhibition. In L.E. cells it was detected in some of the engulfing polymorphs but was only faintly visible, if at all, in the engulfed L.E. body itself. When leukocyte nuclei, separated from cytoplasm by freezing, were similarly treated with quinacrine, a faint characteristic yellow fluorescence could often be observed but this diminished greatly after washing them. This suggests that, while most of the quinacrine was not tightly bound to the nuclear material, a trace may have remained.

3. EFFECT OF QUINACRINE ON PSEUDOPOD FORMATION AND PHAGOCYTOSIS. Leukocytes and plasma were obtained from heparinized (0.025 mg. per ml.) fresh, normal blood after the erythrocytes had been allowed to settle. Quinacrine was added to make the following plasma concentrations: 0.2, 0.4 and 0.6 mg. per ml. of the mixture. The remainder was used as a control. A drop of each mixture was examined "blind" under a cover-slip by phase contrast microscopy. In each case 100 leukocytes were counted and the number of inactive cells noted. Endpoints for phagocytizing ability and presumably viability were based on those given by Tullis[13] and were as follows: Cells with grossly irregular margins and active pseudopods were considered live and capable of ingesting L.E. bodies. Immotile, globular cells were considered inactive or dead and incapable of ingesting L.E. bodies. (Possibly the usual percentage of lymphocytes would also register as "dead" by these criteria.) We also counted as inactive those globular polymorphs showing single, small, smooth elliptical bulges, which slowly formed and subsided, since it seemed inconceivable that such feeble attempts at pseudopod formation could possibly engulf an L.E. body although, theoretically, such cells might still absorb starch or carbon granules, or bacteria. Cytoplasmic granular motion was not taken into consideration as evidence of viability. Typical changes in leukocyte morphology under quinacrine are shown in Figs. 1 and 2.

Using these criteria, observations were made immediately and every half hour for 4 hours. Control and 0.2 mg. per ml. quinacrine specimens showed no significant variation from an average of 85% viable cells over the 4 hours. Towards the end of the period, however, there was less pseudopod activity in the 0.2 mg. per ml. quinacrine group. On the other hand, almost immediately, at the end of one-half hour, and subsequently, the 0.4 mg. per ml. quinacrine concentration showed only 10% active cells, and the 0.6 mg. per ml. concentra-

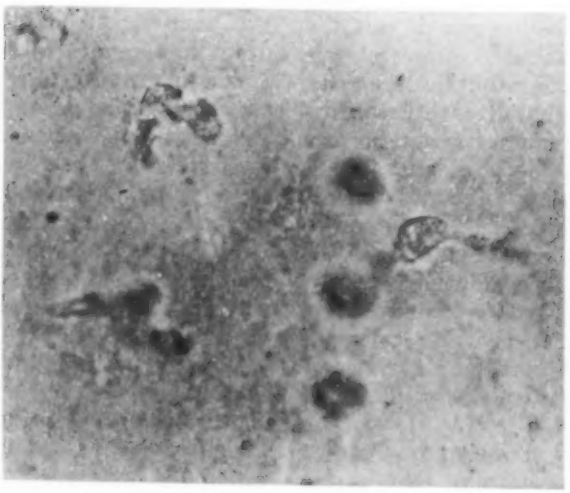

Fig. 1.—Three normal, fresh leukocytes in their own plasma at room temperature. Note irregular outlines and pseudopods, and compare with 3 erythrocytes (slightly out of focus). Magnification × 910.

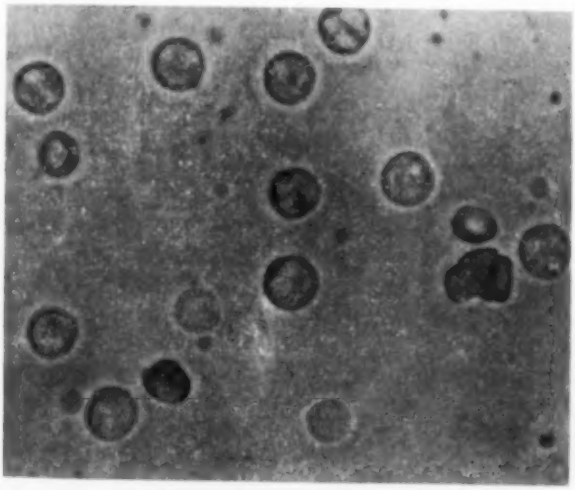

Fig. 2.—Leukocytes from the same preparation as those in Fig. 1 shortly after quinacrine 0.4 mg. per ml. has been added. Note globular outlines and absence of pseudopods. Magnification × 910.

tions, none. Thus, 0.4 mg. per ml. seemed to be the critical concentration of quinacrine at which active polymorphonuclear motion, and presumably phagocytosis, is almost completely arrested. In all our other experiments, when frank inhibition of L.E. formation occurred, it almost invariably did so at the 0.4 mg. level or above.

In the following three experiments we endeavored to isolate the action of quinacrine to each of the three possible sites at which it could, theoretically, block L.E. cell formation, that is: the serum, the cell nucleus and phagocytosis. We took as our end-point simply the presence or absence of typical L.E. cells.

4. ATTEMPT TO BLOCK THE L.E. SERUM FACTOR WITH QUINACRINE. Quinacrine was added to potent L.E. serum to make the following concentrations: 0.1; 0.2; 0.4 and 0.6 mg. per ml. of the mixture. These were incubated together at 37° C. for 40 minutes. In addition, in two instances, concentrations of 1 mg. per ml. were prepared and incubated for 24 hours. Control serum was treated likewise except that no quinacrine was added. If quinacrine *can* react with L.E. serum factor irreversibly to inactivate it, this should now have taken place and the serum factor should be inert. (Our findings in Experiment 1 are against such a reaction, but not conclusively so.)

Fresh, whole, normal blood was now added in the ratio of 4 ml. of blood to 1 ml. of both control and test sera. This supplied live phagocytes and, at the same time, the 4 to 1 dilution had the important effect of reducing the final quinacrine concentrations to 0.2 mg. per ml. and below. These concentrations are ordinarily too weak completely to inhibit phagocytosis. On the other hand, a 4:1 dilution of L.E. serum factor does not impair its ability to form L.E. cells. (This has been noted by others and was confirmed by us in a separate experiment.)

The mixtures of fresh blood and L.E. sera were then added as hanging-drop preparations to smears of dried leukocytes in order to assure an ample supply of dead leukocytes from which L.E. cells could be formed if the mixture still contained any active L.E. serum factor. The hanging-drop and substrate were incubated together for 2 hours. Using this modification of the Snapper-Nathan ring technique, slides were prepared, stained and searched for 10 minutes each, for L.E. cells.

L.E. cells were found in all preparations; that is, in the controls, and in all the serial concentrations of quinacrine-treated sera, including the two which had been incubated for 24 hours. An identical series, using heparinized blood (0.025 mg. per ml.) instead of fresh blood without anticoagulant as above, gave precisely the same results except that the yield of L.E. cells was consistently higher.

Since L.E. cell formation occurred in both test and control groups, it seems clear that, under these experimental conditions, quinacrine did *not* inactivate the L.E. serum factor. Only if L.E. cell formation had been blocked could other factors such as dilution of the L.E. serum factor, quinacrine inhibition of phagocytosis, or quinacrine protection of L.E. bodies be considered as a possible explanation. But, inhibition did *not* occur.

5. PRODUCTION OF L.E. CELLS FROM ISOLATED LEUKOCYTE-NUCLEI. In this experiment, nuclei, separated from their cytoplasm by freezing, were the main object of our attention. Nuclear material so obtained is known to react with L.E. serum factor (German and Huber[4], Miescher and Fauconnet[8]). As will be seen in the procedures described below, several washings were needed in order to remove cytoplasmic debris, free

quinacrine and free L.E. serum factor from the leukocyte nuclei. We found dextran in saline most suitable for this purpose. It is, therefore, important to note that collateral studies showed that dextran neither caused nor inhibited L.E. cell formation, nor did it prevent the inhibitory action of quinacrine, and so may be regarded as an inert substance in this experimental situation.

The buffy coat from normal blood, heparinized as before, was put in eight times its volume of 6% dextran in normal saline, mixed, divided into two equal parts and refrigerated at 0° C. or below for 24 hours. It was then allowed to thaw at room temperature and after being centrifuged, the supernatant was decanted in order to get rid of most of the cytoplasmic and other debris. The remaining "button" was reconstituted in dextran-saline solution to a volume of 1 ml. Microscopic examination of its residue showed discrete nuclear bodies, rare intact leukocytes, no L.E. cells and only traces of debris.

Quinacrine hydrochloride was now added to one tube to make a concentration of 0.6 mg. per ml. and the other tube was kept as a control. Both tubes were then shaken, incubated at 37° C. for 1 hour, again shaken, centrifuged and the supernatant decanted. The residual "button" of nuclear material was less than 0.4 ml. in volume, and on microscopic examination consisted mainly of discrete nuclear bodies. Those which had been quinacrinized fluoresced with a slightly yellow color which suggested the presence of bound quinacrine. Theoretically, traces of free quinacrine may also have been present, but these would definitely have been too little to inhibit subsequent phagocytosis.

If under these conditions, quinacrine is capable of reacting chemically with nuclear material, and if this reaction protects nuclear material against L.E. serum factor, this should now have taken place and the quinacrinized nuclei should no longer be capable of playing their role in L.E. cell production. It is to be noted that no washing or dilution was done at this point so that any quinacrine bound to nuclei would remain there until exposed to the L.E. serum factor.

Potent L.E. serum (0.6 ml.) was now added to each "button," mixed, and incubated at 37° C. for 1 hour, again shaken, then centrifuged and the supernatant decanted. The "buttons" were next washed with dextran-saline solution as before and, lastly, with cell-free plasma from their original donor. The residue was used as a substrate. For all practical purposes, this residue should now be free of both unattached L.E. factor and of free quinacrine. In the control, the L.E. factors should be firmly bound to nuclear material, and, in the quinacrinized specimen, no active L.E. factor should be present if quinacrine really has the power of preventing its interaction with nuclear material.

Material from both buttons was now smeared on clean glass slides and, before they were dry, fresh, normal whole blood, which had been found to be free of L.E. cells, was added in hanging-drop preparations in order to supply live, phagocytosing leukocytes. After incubation for 2 hours, the stained residue was examined for L.E. cells, by the same technique as previously.

A consistently good yield of L.E. cells was found in all slides, of both control and quinacrinized origin. A repeat study, using the same techniques except that the concentration of quinacrine was 1.0 mg. per ml. instead of 0.6 mg. per ml., also produced a consistently good yield of L.E. cells on all slides, the number of cells being

about the same for both test and control groups.

Thus we conclude that, under these experimental conditions, prior exposure of leukocyte nuclei to quinacrine, in more than adequate concentrations for inhibition, did *not* prevent subsequent interaction with L.E. serum factor and, therefore, did not inhibit L.E. cell formation.

6. INHIBITION OF PHAGOCYTOSIS BY QUINACRINE. In the two preceding experiments, good evidence has been obtained that quinacrine does not inactivate the L.E. serum factor nor protect the nuclei of leukocytes against attack by this factor. But inhibition of pseudopod formation has already been demonstrated in experiment number 3, so that, by exclusion, this seems most likely to be the real cause of L.E. cell inhibition. Nevertheless, it was thought worth while to test this possibility in the same type of situation which was used in experiments 4 and 5.

Live, normal leukocytes from minimally heparinized blood were added in equal volume to L.E. serum, mixed, and, after about 1 minute placed in a refrigerator at 0° or below. After 24 hours the mixture was thawed in a water bath at 37° C., centrifuged, and the residue, both washed and unwashed, was used as a substrate. A stained sample showed the residue to consist of numerous nuclear bodies and some debris, but no L.E. cells. Apparently the L.E. bodies had been spared because the cold prevented their phagocytosis. The L.E. serum factor is presumed to be bound to the nuclei, so that they may be regarded as L.E. bodies.

A hanging-drop of fresh, normal blood, to which quinacrine had been added in the same concentrations as in experiment number 4, was now added to the substrate as a source of live leukocytes, incubated for 2 hours and examined for L.E. cells by the same technique as before.

Controls of nonquinacrinized whole blood in hanging-drop preparations yielded large numbers (up to 110) of L.E. cells per slide. These must have been derived from interaction of live leukocytes in the hanging-drop with the nuclei on the substrate. However, the preparations containing quinacrine showed no L.E. cells at all at concentration of 0.4 mg. per ml. and above, and only 2 to 4 L.E. cells per slide at concentrations of 0.2 mg. per ml.

Since quinacrine in 0.4 mg. per ml. is expected to inhibit phagocytosis, and since our previous experiments failed to show inhibitory action directly on serum factor or on isolated cell nuclei, we conclude that the inhibition of L.E. cell formation was most likely due to a quinacrine action impairing pseudopod formation and phagocytosis.

The results of experiments 4, 5 and 6 are presented in Table 1. It is to be noted that our findings are based on a qualitative end-point, namely, the simple presence or absence of L.E. cells, irrespective of the number present. Quantitative evaluations, based on the number of L.E. cells in each preparation, can seldom be relied on because of unknown and uncontrollable factors such as thickness of the preparation, or, possibly, variations in speed of clotting with consequent variations in the availability of free, viable leukocytes. Our sample was not large enough to permit statistical appraisal of the variations, and so no conclusions could be drawn, except that there was a possible hint of a significant reduction in the number of L.E. cells at the 0.2 mg. per ml. concentration.

COMMENT. Reviewing the above data, we feel that a strong case has been made for suppression of phagocytosis being the main, and probably the sole, cause of quinacrine blocking of L.E.

cell formation. We do not imply that phagocytosis is specifically inhibited in otherwise healthy leukocytes, but, rather that quinacrine appears to act as a general leukocytoplasmic poison which blocks pseudopod formation and thus prevents leukocytes from engulfing L.E. bodies. If quinacrine exerts any effect at all on either the serum factor or the leukocyte nuclei, it is too subtle to be detected by using L.E. cell formation as an end point.

Our *in vitro* findings do not, we believe, throw any light on the pharmacological mode of action of quinacrine against the connective-tissue diseases. For one thing, the concentration of quinacrine in the blood of patients receiving the drug is on the order of 0.0001 mg. per ml., whereas the inhibitory effect which we observed began at 0.2 mg. per ml. and was definite at 0.4 mg. per ml. and above. Furthermore, it is doubtful if one can compare the effects of traces of quinacrine acting in the patient's blood over months and even years with the brief exposure to high concentrations of quinacrine *in vitro* for a few hours. Also, it seems unlikely that damage to leukocytes,

TABLE 1

| *Experiment 4* Concentration of Quinacrine mg./ml. | | | *Experiment 5* | | *Experiment 6* | |
|---|---|---|---|---|---|---|
| *Serum* | *Hanging Drop* | *L.E. Cells* | *Concentration of Quinacrine Bathing Nuclei of Leukocytes mg. /ml.* | *L.E. Cells* | *Concentration of Quinacrine in Fresh Blood with Live W.B.C. mg. /ml.* | *L.E. Cells* |
| 0 | 0 | + | 0 | + | 0 | + |
| 0 | 0 | + | 0 | + | 0 | + |
| 0 | 0 | + | 0 | + | 0 | + |
| 0 | 0 | + | 0 | + | 0.2 | + |
| 0.1 | 0.02 | + | 0.6 | + | 0.2 | + |
| 0.1 | 0.02 | 0 | 0.6 | + | 0.4 | 0 |
| 0.2 | 0.04 | + | 0.6 | + | 0.4 | 0 |
| 0.2 | 0.04 | + | 0.6 | + | 0.6 | 0 |
| 0.2 | 0.04 | + | 1.0 | + | 0.6 | 0 |
| 0.2 | 0.04 | + | 1.0 | + | 0.8 | 0 |
| 0.4 | 0.08 | + | 1.0 | + | 0.8 | 0 |
| 0.4 | 0.08 | + | 1.0 | + | 1.0 | 0 |
| 0.4 | 0.08 | + | 1.0 | + | 1.0 | 0 |
| 0.4 | 0.08 | + | | | | |
| 0.6 | 0.12 | + | | | | |
| 0.6 | 0.12 | + | | | | |
| 1.0 | 0.2 | + | | | | |
| 1.0 | 0.2 | + | | | | |
| 1.0 | 0.2 | + | | | | |
| 1.0 | 0.2 | + | | | | |

*Experiment 4.* Test for blocking of L.E. serum factor. L.E. serum was incubated with ascending concentrations of quinacrine, and the product then diluted in the hanging drop preparation to make concentrations of 0.2 mg. per ml. and below, which are too weak to inhibit phagocytosis.

*Experiment 5.* Test for protection of L.E. bodies. Leukocyte nuclei were incubated with quinacrine in 0.6 and 1.0 mg. per ml. concentration, washed and then exposed to active L.E. serum, again washed and then mixed with live leukocytes.

*Experiment 6.* Test for blocking phagocytosis. L.E. serum added to live leukocytes and quickly frozen to prevent phagocytosis of L.E. bodies. Quinacrine added in serial concentrations to fresh, live leukocytes to test their ability to phagocytose the L.E. bodies.

which is the only property of quinacrine which we have demonstrated here, would benefit either rheumatoid arthritis or systemic lupus erythematosus (S.L.E.).

While the L.E. serum factor may possibly play a role in producing the clinical manifestations in certain phases of S.L.E., it must be remembered that it is not always demonstrable in patients with clinically active disease, so that too much cannot be claimed for the etiological significance. However, if inactivation of the serum factor could be shown to take place and to thereby benefit the disease, the experimental designs which we have described might be useful for screening drugs *in vitro*. For this, the first step would be to test for simple blocking of L.E. cell formation by incubating the drug with whole L.E.-cell-positive blood. If a given drug should block L.E. cell formation, then our methods could be used to find out whether the blocking takes place at the serum level, the nuclear level or by inhibition of phagocytosis.

**Summary.** 1. Quinacrine in concentrations of 0.4 mg. per ml. and up blocks L.E. cell formation by poisoning leukocytes, arresting pseudopod formation and thus preventing them from engulfing L.E. bodies.

2. Incubation of quinacrine with L.E. serum does not inactivate the L.E. factor, neither are leukocyte nuclei protected from attack by the L.E. serum factor by prior exposure to quinacrine.

3. As judged by ultraviolet light fluorescence, quinacrine is concentrated in the cytoplasm of leukocytes and only slightly in leukocyte nuclei and L.E. bodies. Electrophoretic study suggested that it may have an affinity for serum globulins but that it is easily displaced from them.

4. The L.E. cell may be useful in screening drugs for ability to inhibit the L.E. serum factor. If L.E. cell formation is blocked, our methods can determine whether the block is at the serum or cellular level.

5. Our *in vitro* studies shed no light on the antirheumatic action of antimalarials *in vivo*.

ADDENDUM: Since the above article was submitted for publication, we have investigated the inhibiting properties of several other antimalarials. We find that chloroquin (Aralen), hydroxy-chloroquin-sulfate (Plaquenil), amodiaquin (Camoquin) and amopyroquin (Propoquin) all block L.E. cell formation in fresh L.E. blood and all inhibit phagocytosis, but none of them inhibits the L.E. serum factor itself. The concentrations necessary for this were all somewhat higher than those needed for quinacrine and in some cases were less sharply defined. On the basis of our scant information as to the relative antirheumatic potency of these antimalarials, there seemed to be no relation between this and the concentrations needed to inhibit L.E. cell formation *in vitro*.

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## SUMMARIO IN INTERLINGUA

### Un Studio del Mechanismo per le Qual Quinacrina Inhibi le Formation de Cellulas L.E.

1. Quinacrina in concentrationes de 0,4 mg per ml e plus bloca le formation de cellulas L.E. per invenenar le leucocytos, per arrestar le formation de pseudopodes, e per prevenir los assi de inglobar corpores L.E.

2. Le incubation de quinacrina con sero L.E. non produce un inactivation del factor L.E., e nucleos leucocytic non es protegite contra le attacco del serofactor L.E. per un antecedente exposition a quinacrina.

3. A judicar per fluorescentia a lumine ultraviolette, quinacrina es concentrate in le cytoplasma de leucocytos e solmente levemente in le nucleos leucocytic e in le corpores L.E. Un studio electrophoretic pareva indicar que quinacrina possede un affinitate pro globulinas seral sed que illo es facilemente displaciate ab illos.

4. Le cellula L.E. es possibilemente utile in scrutinar drogas con respecto a lor capacitate de inhibir le serofactor L.E. Si le formation de cellulas L.E. es blocate, nostre methodos pote monstrar si le bloco occurre al nivello seral o al nivello cellular.

5. Nostre studios, effectuate in vitro, non illumina le action antirheumatic de animalariales in vivo.

# THE EFFECT OF LINOLEIC AND LINOLENIC ACID, ESTRADIOL VALERATE AND BETA SITOSTEROL UPON EXPERIMENTALLY INDUCED HYPERCHOLESTEROLEMIA AND THE DEVELOPMENT OF LIPID CHANGES IN THE AORTA OF DOGS

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A search has been made for an agent that would impair absorption of cholesterol so that a lowering of the serum cholesterol concentration might be obtained. It has been postulated that such an agent might decrease the incidence of atherosclerosis in the human and also might conceivably result in reabsorption of cholesterol from atheromatous plaques already formed. Other investigators have studied a number of agents in the rat, chicken and rabbit with somewhat conflicting results; however, some of the substances, under experimental conditions, have apparently exerted an effect upon the development of lipid change in the aortas of the animals studied (Best and Duncan[1], Diller, Woods and Harvey[3], Malinow, Pellegrino and Ramos[5], Page[6], Stalmer, Pick and Katz[7]).

Previous experience with induced hypercholesterolemia in the dog indicates that this animal is less susceptible to the development of atheromatous change than other animals often used for such studies; therefore, it seemed desirable to test the efficacy of some of these agents using the dog as the experimental animal (Creech *et al.*[2], Steiner and Kendall[8]). Previous experiments in this laboratory have indicated that the lyophilized homograft is more susceptible to lipid change than is the host aorta. Consequently, the utilization of an experimental animal in which such grafts have been placed allows comparison between a portion of vessel which is susceptible to these changes and a portion of the normal vessel that is more resistant (Creech *et al.*[2]). Linoleic and linolenic acid, beta sitosterol, and estradiol valerate were selected for study.

**Method of Study.** In each of 20 dogs a lyophilized homograft was placed in the abdominal aorta just proximal to the trifurcation, using nonabsorbable silk suture technique. All of the animals survived the operation. Each was treated with radioactive iodine

*Supported in part by Public Health Grant H-1990

given parenterally in a dose of 1 millicurie per kg. of body weight to ablate the thyroid. Each animal was then fed a specific diet during the remainder of the experiment. This diet consisted of 38% horse meat, 57% kibbles and 5% cholesterol by weight. Exclusive of cholesterol each dog was offered daily 43 gm. of saturated animal fat, 108 gm. of protein, and the total caloric intake was 1951 calories. The animals were divided into 4 groups. Group 1 served as controls. The animals in Group 2 were fed daily 60 gm. of an emulsion of unsaturated fatty acids. The principal constituent of this emulsion was linoleic acid. A lesser amount of linolenic acid was present and Vitamin $B_6$ was also a constituent. One milliliter of estradiol valerate (10 mg.) was administered parenterally to the animals in Group 3 each week, and 45 gm. of beta sitosterol were added daily to the diet of the animals in Group 4. These regimens were continued until the termination of the experiment. Serum concentrations of cholesterol and cholesterol esters were determined prior to treatment and at weekly intervals during the period of study.

At the termination of the experiment each sacrificed animal was examined to note the extent and distribution of vascular lesions. The heart and entire aorta were removed and after fixation in 10% formalin, sections were taken from appropriate areas for microscopic study.

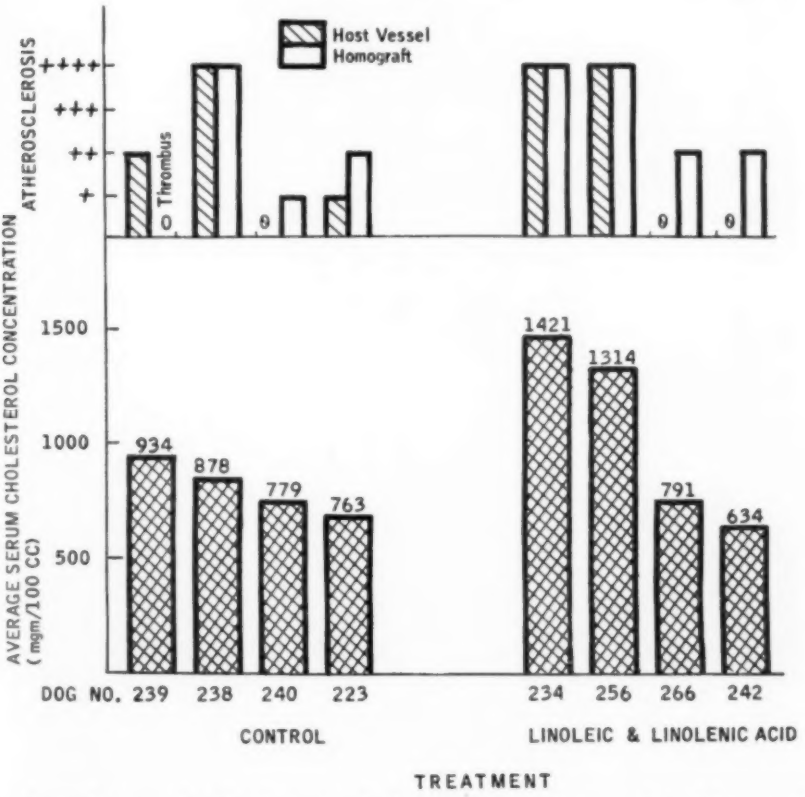


Fig. 1.—A graph comparing development of atherosclerosis in host vessels and homografts as related to average serum cholesterol concentrations in the animals in Groups 1 and 2.

**Results.** One animal in each group survived less than 15 weeks. These were excluded from the study. The remaining 16 survived for periods varying from 22 to 40 weeks. The average

serum cholesterol concentrations in the control animals varied from 763 to 934 mg. per 100 ml. (Fig. 1). All animals developed atheromatous change. In one the change occurred only in the homograft. The graft in Dog 239 was thrombosed but atheromatous change occurred in the host vessel. Lipid change was observed in both the host vessels and the grafts of the remaining two dogs (Fig. 2).

The 4 dogs in Group 2 that were fed the fat emulsion survived for periods from 26 to 38 weeks. The average se-

Fig. 2*a*.—The abdominal aorta of Dog 238 disclosing scattered elongated plaques of atheromatous changes. They are more diffuse and extensive in the graft.

Fig. 2*b*.—Microscopic appearance of the homograft. The newly formed intima is fairly broad with numerous foam cells interspersed. The elastic fibers of the media appear crowded. Weigert's elastic tissue stain × 60.

rum cholesterol concentrations ranged between 634 and 1421 mg. per 100 ml. Two animals developed lipid changes only in the graft while the remaining two, with average serum cholesterol concentrations exceeding 1000 mg. per 100 ml., had extensive atherosclerosis throughout the grafts and host vessels including the coronary arteries (Fig. 3). The most extensive changes noted in this experiment were in these 2 animals (Jordan, DeBakey and Halpert[4]).

The animals in Group 3, treated with

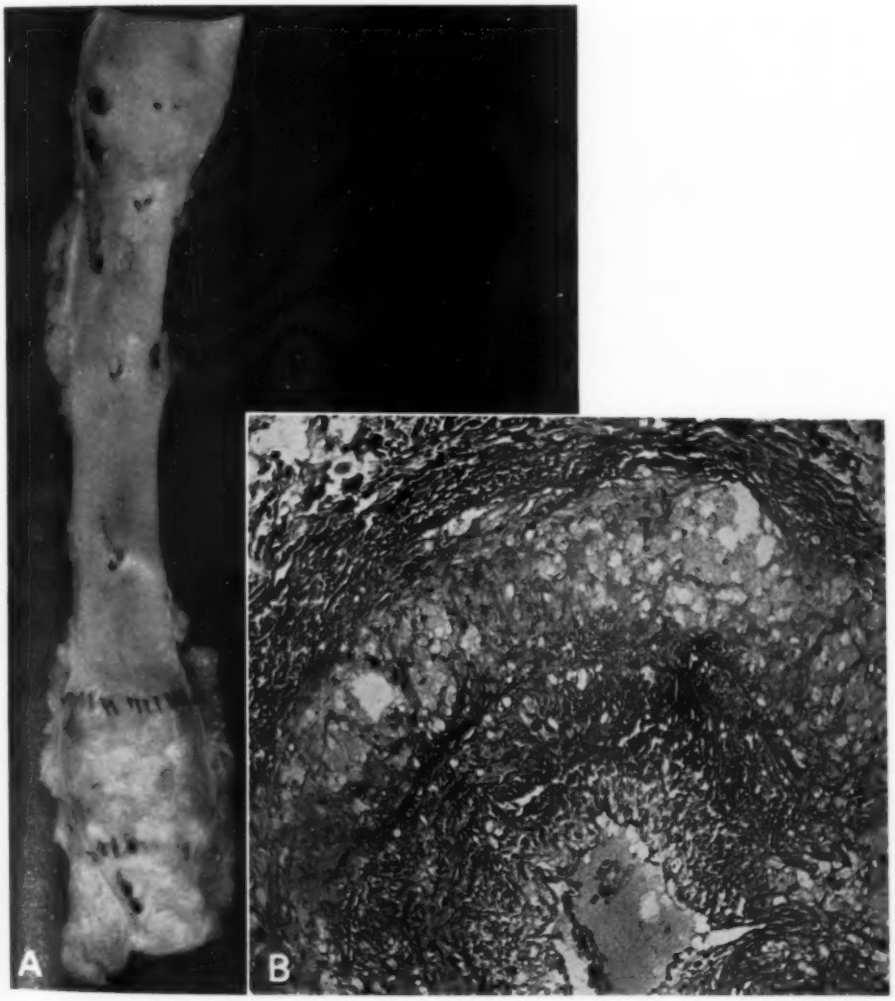


Fig. 3*a*.—The abdominal aorta of Dog 256. Occasional atherosclerotic plaques are noted in the host portion. The changes are diffuse and extensive in the graft.

Fig. 3*b*.—Left coronary artery of Dog 256. Lipid laden large mononuclear cells replace the media. There is broadening of the intima with some lipid containing foam cells in the broadened subintimal layer. Masson's trichrome stain × 100.

estradiol valerate, survived from 22 to 35 weeks and the average serum cholesterol concentrations ranged from 504 to 1056 mg. per 100 ml. (Fig. 4). Atherosclerosis was observed in the grafts and host vessels of 2 of the animals while no changes were observed in the remaining 2 (Fig. 5).

The fraction of cholesterol present in the form of esters was within normal range for each animal. The averages were 60.7%, 70.8%, 71.1% and 71.2%, respectively, for Groups 1 through 4.

**Discussion.** These results indicate that linoleic and linolenic acids do not protect the dog against the development of hypercholesterolemia or the deposition of lipid material in the aorta under the conditions of this experiment. In fact, the average serum cholesterol concentrations in these animals were even greater than in the control animals, as were the vascular

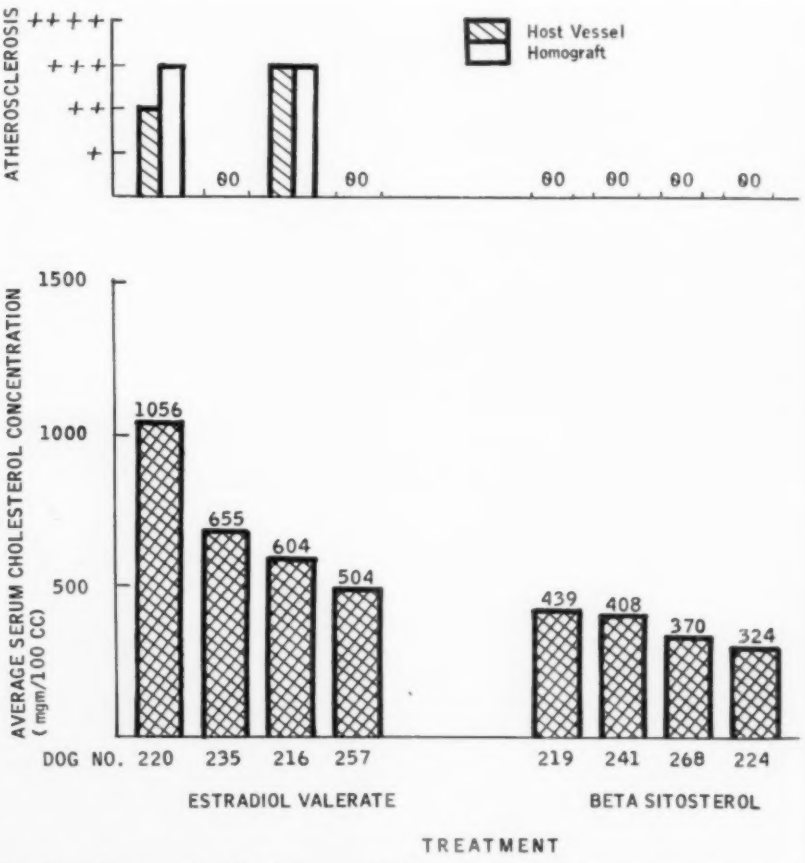


Fig. 4.—A graph comparing development of atherosclerosis in host vessels and homografts as related to average serum cholesterol concentrations in the animals in Groups 3 and 4.

The animals in Group 4 were treated with beta sitosterol and survived from periods of 22 to 37 weeks, but none developed an average serum cholesterol concentration in excess of 439 mg. per 100 ml. No lesions were noted in the grafts or host vessels of any of these animals.

changes (Fig. 6). It should be noted that the animals in this group, however, had a greater caloric intake (approximately 540 calories per day) than the dogs in the other group and this factor may have contributed to increased deposition of lipid material.

The average serum cholesterol concentration for the group of dogs treated with estradiol valerate was 116 mg. less than the average for the control group but in no animal was the average serum cholesterol concentration within normal limits. The incidence of lipid

Fig. 5*a*.—The abdominal aorta of Dog 220. There are occasional small atheromatous plaques in the host portion. These are more numerous along the suture lines. A thin coagulum covers almost half of the intimal surface of the graft.

Fig. 5*b*.—Microscopic appearance of the homograft of Dog 220. A thin coagulum covers the intimal surface. The newly formed intima is composed of loose connective tissue containing strands or islets of large mononuclear cells with foamy cytoplasm. Weigert's elastic tissue stain × 60.

change also was less than observed in the control animals. These data suggest an effect of this drug, but the deviation from the controls is not striking in this small group of animals.

All of the animals in Groups 1, 2, and 3 ate their diet well throughout this experiment. The animals in Group 4, however, failed to eat well and frequently left a significant portion of their daily rations. Attempts at forced feeding were unsuccessful. It was ascertained that the failure to eat was due to the incorporation of beta sitosterol in the diet, for with the omission of this agent there was immediate resumption of appetite and ingestion of all food offered to the animal. Thus the results obtained in animals treated with beta sitosterol cannot be interpreted satisfactorily, for not only did the animals fail to ingest their total dose of beta sitosterol, they also failed to ingest the same amount of cholesterol as did the other animals. Thus the low serum cholesterol concentrations obtained could be explained by simple failure of ingestion of a satisfactory amount of cholesterol. Other investigators have suggested more specific effects of sitosterol but the effect on appetite noted in this experiment was such that it is not possible to arrive at any conclusion concerning other effects of this drug. The absence of lipid change in the aortas and grafts of these animals could be predicted in view of the low average of serum cholesterol concentrations which were maintained.

**Summary.** Four groups of dogs were rendered hypothyroid by the administration of radioactive iodine and fed a high cholesterol diet. Hypercholesterolemia and lipid deposition in the aorta developed in each of the control dogs. Similar changes were noted in a group of animals treated with linoleic and linolenic acids, and in a group treated with estradiol valerate though to a lesser degree in the latter group. In the fourth group treated with beta sitosterol the animals failed to ingest their diet satisfactorily, and total cholesterol intake was less than in other groups. No animal in this group developed lipid change in the host vessel.

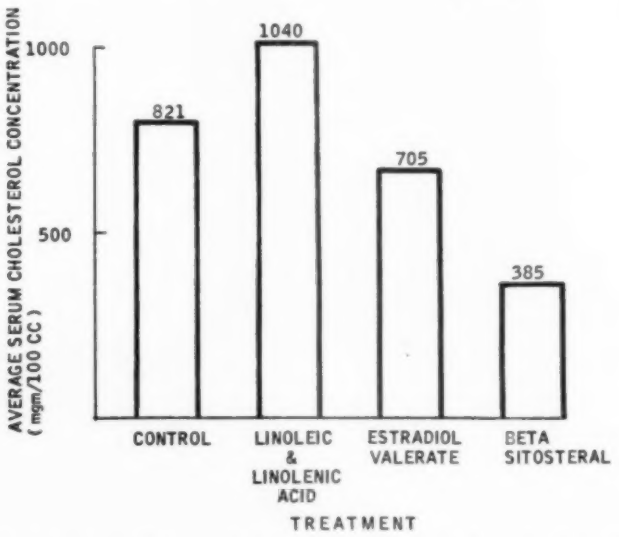


Fig. 6.—Combined averages of serum cholesterol concentrations for animals in Groups 1, 2, 3, 4

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## SUMMARIO IN INTERLINGUA

**Le Effecto de Acido Linoleic e de Acido Linolenic, de Valerato de Estradiol, e de Sitosterol Beta Super un Experimentalmente Inducite Hypercholesterolemia e Super le Disveloppamento de Alterationes Lipidic in le Aorta del Can**

Quatro gruppos de canes esseva rendite hypothyroide per le administration de iodo radioactive e mantenite con dietas a alte contento de cholesterol. Hypercholesterolemia e deposition de lipido in le aorta superveniva in omne le canes de controlo. Simile alterationes esseva notate in un gruppo de animales tractate con acidos linoleic e linolenic e etiam—ben que a grados minus marcate—in un gruppo tractate con valerato de estradiol. In le quarte gruppo, illo tractate con sitosterol beta, le animales non ingereva lor dieta satisfactorimente, e le ingestion total de cholesterol esseva minus que in le altere gruppos. In iste gruppo nulle animal disveloppava alterationes lipidic in le aortas e graffos.

# LIPOPROTEIN ELEVATIONS OF DIABETICS ON TOLBUTAMIDE AS COMPARED TO LIPOPROTEIN LEVELS DURING INSULIN THERAPY: PRELIMINARY OBSERVATIONS*

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A renewed interest in diabetic complications, especially degenerative vascular, has taken place with the widespread use of oral substitutes for insulin. While following patients who were converted from insulin to tolbutamide, the following questions entered our minds: (1) are beta lipoproteins important in vascular degenerations in diabetes; (2) although blood sugars are within normal limits while on tolbutamide, are the intermediate products of metabolism "normalized;" (3) are patients who were formerly controlled on insulin more prone to vascular complications now that they are maintained on tolbutamide?

In this study, we undertook to compare the levels of cholesterol, alpha, beta, and gamma lipoprotein percentages in patients who were on insulin as against these same patients while on tolbutamide.

**Material and Methods.** Patients were selected from the Diabetic Clinic of Abington Memorial Hospital. All were of maturity onset type of diabetes and were taking between 15 and 40 units of insulin (Table 1). All were controlled on insulin with blood sugars between 60 and 180 mg. per 100 ml. and had been maintained on standard diabetic diets of 1600 to 1800 calories. Baseline fasting blood sugars, cholesterol, alpha, beta, and gamma lipoprotein percentages were determined while on insulin. After one and 6 months on tolbutamide the above studies were repeated. All determinations were performed on blood drawn from the same venipuncture and blood studies were performed within 2 hours after the blood was drawn. The blood sugar determinations did not show a statistically significant variation at the time of electrophoretic and cholesterol determinations (Table 2). Of great importance is the fact that all patients were ambulatory with no manifestations of major illness which would complicate the studies.

The blood sugar determinations were performed on the Auto-Analyser. The cholesterol and esters were determined by a modified Bloor method.

*Presented in part at American Diabetes Association Meeting, Miami Beach, June, 1960.

Electrophoresis was performed in a Spinco-Durrum type cell using barbital buffer (2.76 gm. diethyl barbituric acid, 15.40 gm. Na diethyl barbiturate dissolved in 1000 ml. of distilled water) of pH 8.6 and ionic strength 0.075. Twenty lambda of serum were placed on S & S strips #2043-A by a strip applicator (Spinco Co.). The strips were placed in the cell and a constant current of 17 ma applied for 2 hours. The strips were then dried for 10 minutes at 120 degrees C. Staining was performed with Sudan Black B dye as described by Jencks and Durrum[11]. Rinsing was done in 50% ethyl alcohol until a light blue tint remained on the background paper. Photoelectric scanning (using a Spinco Analytrol with B-5 cam) was utilized to determine the percentage of lipoprotein fractions.

**Results.** A. AFTER 1 MONTH TOLBUTAMIDE. Table 1 reveals that the percentage of lipid bound to the beta-globulin was elevated in 11 out of 13 cases. In cases 8 and 11 respectively there was no change and a minor decrease. The mean difference in percent of lipid bound to beta-globulin as compared to insulin control was $+9 \pm 1.79\%$ ($t = 5.01$, p less than 0.01) in 12 patients (patient 1 was not considered because of the marked elevation of his beta-lipoprotein percent).

As previously mentioned, sugar determinations did not vary significantly from time of insulin to 1- or 6-month tolbutamide examinations. The cholesterol variations after one month revealed no significant tendency to change in either direction.

B. AFTER 6 MONTHS ON TOLBUTAMIDE. In 11 out of 11 patients there were increases in percent of lipid measured as that bound to beta-globulin. Patient 2 was dropped from the study on his own request and patient 9 expired. During statistical analyses, patient 13 was eliminated due to her great elevation of the beta-lipoprotein fraction. Therefore, the mean difference in percent of lipid bound to beta-globulin as compared to insulin control was $+21 \pm 3.41\%$ ($t = 6.14$) in 10 patients. Again cholesterol values revealed no definite tendency to increase or decrease.

In comparing the difference between the two means, there was a rise of $+12 \pm 4.05\%$ ($t = 2.96$, p less than 0.01). It is, therefore, evident that there was a significant increase between the 1- and 6-month periods.

**Discussion.** It is a well-known fact that as lipid and protein combine to become a lipoprotein, both lose their original properties and take on new chemical and physical properties (Walker and Kinsell[23]). These lipids which migrate with the various globulin partitions consist mainly of cholesterol, triglycerides, and phospholipids. They are designated either as alpha, beta, or even gamma lipoproteins depending upon the globulin fraction with which they are transported. The majority of triglycerides are transported as chylomicra but the cholesterol, phospholipids and remaining triglycerides are transported as lipoproteins. The high $S_f$ lipoproteins and chylomicra are dispersed into smaller particles and free fatty acids by the action of heparin via a lipoprotein lipase mechanism (lipolytic enzymes) with a marked reduction of turbidity of the serum. Indeed, these fatty acids are dependent upon albumin for their transport and in the absence or decrease of albumin as occurs in nephrotic syndrome there occurs a backlog of fatty acids. Consequently, the entire lipoprotein breakdown scheme is paralyzed with resulting hyperlipemia (Dole[6], Duncan[7], Ehrich[8]). Some investigators feel the lipemia in nephrotic syndrome is due to the increase in the synthesis of lipoproteins by the liver.

In diabetes the degree of lipemia depends on the success of insulin therapy in controlling carbohydrate metabolism. More recent work on clearing of lipemic serum has shown nonsulfated mucopolysaccharides (PDHA) of great-

TABLE 1

| *Patient* | *Sex* | *Age* | *Duration of Diabetes (years)* | *Insulin dose before conversion* | *Lipoprotein % on Insulin (0 month)* | *Lipoprotein % on Tolbutamide (1 month)* | *Lipoprotein % on Tolbutamide (6 months)* | *% increase of β-lipoprotein in 1 month compared to 0 month* | *% increase of β-lipoprotein in 6 months compared to 0 month* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 72 | 1.5 | 35 | α 26<br>β 67<br>γ 7 | α 3<br>β 93<br>γ 3 | α 8<br>β 87.8<br>γ 4 | 39 | 31 |
| 2 | M | 60 | 9 | 40 | α 30<br>β 65<br>γ 4 | α 19<br>β 75<br>γ 6 | | 15 | |
| 3 | F | 64 | 8 | 30 | α 14<br>β 76<br>γ 10 | α 10<br>β 83<br>γ 7 | α 6<br>β 88<br>γ 6 | 8 | 16 |
| 4 | F | 60 | 3 | 25 | α 16<br>β 72<br>γ 12 | α 15<br>β 83<br>γ 2 | α 3.7<br>β 93.1<br>γ 3.7 | 15 | 30 |
| 5 | F | 65 | 9 | 25 | α 27<br>β 71<br>γ 1 | α 15<br>β 79<br>γ 6 | α 7.6<br>β 88.8<br>γ 6 | 12 | 25 |
| 6 | F | 67 | 4 | 15 | α 19<br>β 73<br>γ 8 | α 12<br>β 83<br>γ 5 | α 1.4<br>β 93.9<br>γ 4.4 | 17 | 29 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 6 | F | 67 | 4 | 15 | $\beta$ 75<br>$\gamma$ 8 | $\beta$ 83<br>$\gamma$ 5 | $\beta$ 93.9<br>$\gamma$ 4.4 | 17 | 29 |
| 7 | F | 67 | 9 | 20 | $\alpha$ 21<br>$\beta$ 72<br>$\gamma$ 7 | $\alpha$ 12.5<br>$\beta$ 84<br>$\gamma$ 3 | $\alpha$ 9.8<br>$\beta$ 88.5<br>$\gamma$ 1.5 | 0 | 23 |
| 8 | F | 56 | 1 | 15 | $\alpha$ 27<br>$\beta$ 68<br>$\gamma$ 4 | $\alpha$ 28<br>$\beta$ 68<br>$\gamma$ 3.5 | $\alpha$ 9.8<br>$\beta$ 87.7<br>$\gamma$ 2.4 | 8 | 29 |
| 9 | F | 84 | 1.5 | 40 | $\alpha$ 21<br>$\beta$ 79<br>$\gamma$ 0 | $\alpha$ 14<br>$\beta$ 85<br>$\gamma$ 1 | | 7 | |
| 10 | F | 83 | 5 | 20 | $\alpha$ 21<br>$\beta$ 72<br>$\gamma$ 6 | $\alpha$ 18<br>$\beta$ 77<br>$\gamma$ 5 | $\alpha$ 14<br>$\beta$ 78<br>$\gamma$ 7 | 1 | 8 |
| 11 | M | 63 | 4 | 40 | $\alpha$ 3<br>$\beta$ 79<br>$\gamma$ 18 | $\alpha$ 8.5<br>$\beta$ 79.5<br>$\gamma$ 12 | $\alpha$ 2.9<br>$\beta$ 95<br>$\gamma$ 1.4 | 1 | 20 |
| 12 | F | 71 | 4 | 35 | $\alpha$ 3<br>$\beta$ 85<br>$\gamma$ 12 | $\alpha$ 14<br>$\beta$ 84<br>$\gamma$ 5 | $\alpha$ 10<br>$\beta$ 85<br>$\gamma$ 5 | −1 | 0 |
| 13 | F | 55 | 5 | 35 | $\alpha$ 6.7<br>$\beta$ 53<br>$\gamma$ 40 | $\alpha$ 1.3<br>$\beta$ 59.5<br>$\gamma$ 39.2 | $\alpha$ 3<br>$\beta$ 90<br>$\gamma$ 1 | 12 | 70 |

(1) After 1 month mean difference in per cent of lipid bound to beta globulin ($\beta$-lipoprotein) $= +9 \pm 1.79\%$ ($t = 5.01$, $p<.01$) 12 patients

(2) After 6 mo. mean difference $= +21 \pm 3.41\%$ ($t = 6.14$, $p<.01$) 10 patients

(3) Difference between the means (1 and 6 months) $+12 \pm 4.05\%$ ($t = 2.96$, $p<.01$)

er benefit than heparin in lipemias induced by the lipid mobilizing hormone (LMH). The role of PDHA is to block the peripheral effect of LMH on omental fat stores while heparin activates lipoprotein lipase. Apparently diabetics do not have elevated LMH levels (Hashim[10], Searle *et al.*[17], Wolff and Salt[25]).

When adequate carbohydrate utilization is insured and when the blood sugar is below 200 mg. per 100 ml. the levels of beta-lipoprotein, cholesterol and nonesterified fatty acids will decrease. Usually there is a poor correlation between blood sugar and cholesterol values. A most important fact is that there is no simple form of lipid pattern in diabetes mellitus (Foster and Siperstein[9], Joslin, Root, White and Marble[12], Lowry and Barach[15]).

In females, there has been reported a constant correlation between atherosclerotic complications and elevated lipid levels in Kimmelstiel-Wilson disease, retinopathy, and other degenerative vascular complications. Rigid control of the diabetic state reduced the hyperlipemia and diabetic complications (Krahl[14]). Similar studies have been carried out in pregnant diabetics (Ditzel and Moinat[4]). Even without acidosis, poorly controlled diabetics revealed elevated cholesterol and $S_f$ 0-12 and $S_f$ 100-400 lipoproteins (Steiner and Williams[20]). Recently lipoprotein levels have been correlated with the sludging and aggregation of erythrocytes (Ditzel and Moinat[5]).

At this point, it is necessary to mention some of the proposed actions of tolbutamide: (1) increase endogenous insulin; (2) decrease glucagon production; (3) facilitation of normal hepatic processes related to insulin binding; (4) decrease formation of glucose through inhibition of phosphorylase; (5) increase hepatic enzymes which promote glycogen formation and phosphogluconate shunt; (6) inhibition of insulin antagonists and (7) displacement of insulin from nonspecific and noneffectual linkages (Beber and Beber[1], Craig and Maller[3], Joslin *et al.*[12], Knox and Doenges[13], Searle *et al.*[17], Seltzer and Smith[19], Strisower *et al.*[21]). Of the above theories none fully appears to duplicate

TABLE 2

| *Patient* | *Fasting Blood Sugar 0 Months* | *Fasting Blood Sugar 1 Month* | *Fasting Blood Sugar 6 Months* |
|---|---|---|---|
| 1 | 145 (200) | 150 (248) | 107 (196) |
| 2 | 140 (—) | 140 (—) | Dropped out |
| 3 | 146 (310) | 140 (295) | 137 (252) |
| 4 | 188 (230) | 117 (215) | 154 (218) |
| 5 | 160 (289) | 135 (263) | 167 (254) |
| 6 | 95 (305) | 81 (285) | 120 (316) |
| 7 | 107 (295) | 112 (340) | 147 (318) |
| 8 | 165 (232) | 190 (218) | 158 (257) |
| 9 | 100 (259) | 113 (320) | Deceased |
| 10 | 165 (237) | 128 (235) | 122 (195) |
| 11 | 84 (212) | 130 (218) | 180 (240) |
| 12 | 53 (315) | 53 (304) | 80 (297) |
| 13 | 95 (275) | 102 (298) | 120 (275) |

*Values in brackets following blood sugars represent serum cholesterol in mg. per 100 ml. determined at the same time of sugar determination.

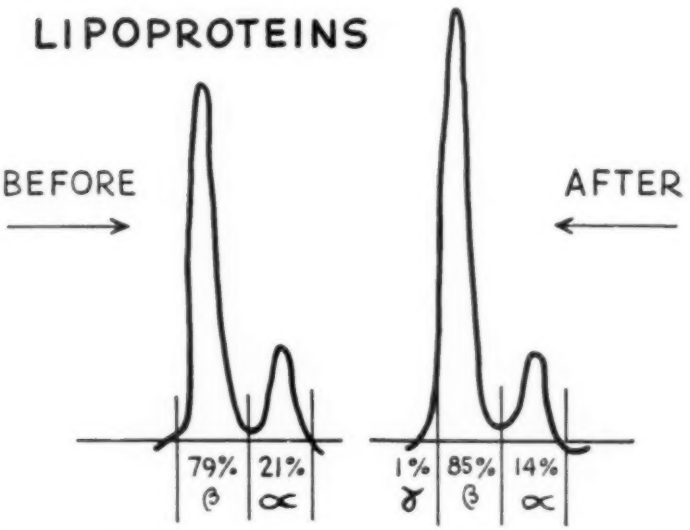


Fig. 1.—Sudan B Black Lipoprotein Electrophoresis: pattern on left during insulin therapy; on right pattern one month after tolbutamide revealing increase from 79% to 85% β-lipoprotein.

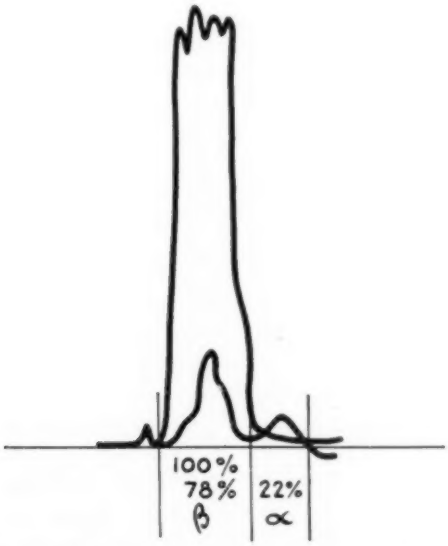


Fig. 2.—Sudan B Black Lipoprotein Electrophoretic Pattern of a child in diabetic acidosis (cholesterol 1500 mg. per 100 ml., $CO_2$ 3 mEq. per L.), revealing β-Lipoprotein 100%. Control superimposed shows 78% β-lipoprotein and 22% alpha lipoprotein.

insulin action except (1). The decrease in glucose levels has been reported due to lowering of endogenous production rather than increased rate of removal of glucose, (Craig and Maller[3], Mann[16]). Noted also is the difficulty in assessing insulin-like activity in peripheral blood after tolbutamide and correlating it with its hypoglycemic effect (Seifter *et al.*[18]). In any case, the ability of oral substitutes to decrease NEFA and total lipids is dependent upon the fact that oral substitutes apparently decrease the elevated blood sugar levels (Comportamento[2], Tornow *et al.*[22]). However, one with an inquisitive mind might ask if the oral substitutes are truly a substitute for insulin or merely a hypoglycemic agent *in vivo* with no direct effect on lipids aside from their hypoglycemic effect with secondary reduction in lipid levels.

Because of these considerations we became interested in the effect of tolbutamide on lipoproteins. As previously stated, there appears to be a correlation between control, lipoproteins and complications. Therefore, a patient on tolbutamide therapy may not be under as accurate control of his diabetic state although his blood sugars appear just as controlled while on tolbutamide as when compared to insulin therapy. In our preliminary work it has been shown that the percentage of beta-lipoproteins has not been as well-controlled in diabetics when on tolbutamide as against these same patients when given insulin. The cholesterols have followed no such pattern.

Although in other reports lipoproteins and other intermediate products of fat metabolism are normalized after tolbutamide, these studies were performed in diabetics without comparing their levels while on insulin (Comportamento[2]). In our study the patients while on insulin served as their own controls and revealed less control of lipoproteins during tolbutamide therapy, even though blood sugars were just as controlled. Indeed, patient's lipoprotein patterns while on insulin differed very little from normal patterns.

What the long-term effect will be on diabetic complications is yet to be answered. If the beta-lipoproteins and their proportion to other lipoproteins are directly related to vascular complications, then tolbutamide treated patients may be more prone to diabetic vascular complications as compared to these same patients when on insulin.

Because of our results in this preliminary report, it is apparent that a more intensive survey be attempted. In much the same manner we are now determining lipoproteins using Neutral Fat 7B dye, total lipids, triglycerides, phospholipids, nonesterified fatty acids, cholesterol and cholesterol esters before and after conversion to tolbutamide. Perhaps a more distinct picture can be obtained in such patients after conversion to tolbutamide from insulin and help answer the question whether tolbutamide is an adequate "substitute" for insulin.

**Summary.** A significant increase in the percentage of beta-lipoprotein measured electrophoretically was found in 13 patients when switched from insulin to tolbutamide, although sugars were as well controlled with tolbutamide in recommended doses. An increase in the lipid bound as beta-globulin fraction of $+9 \pm 1.7\%$ (mean difference) occurred after one month on tolbutamide as compared to insulin control in the same patients. After 6 months, the increase compared to insulin control was $+21 \pm 3.41\%$ (mean difference) and the difference between the means of one- and 6-months was $+12 \pm$

4.05%. Cholesterol values showed no definite tendency to increase or decrease.

Therefore, the question arises whether there was adequate control of the entire diabetic state in order for such a shift of lipoprotein pattern to occur. Whether such a shift will affect vascular degeneration is yet to be determined. Further lipid studies are now under way in tolbutamide treated patients. Preliminary studies reveal more adequate control of the entire diabetic state with insulin.

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## SUMMARIO IN INTERLINGUA

### Elevationes de Lipoproteina in Diabeticos sub Tractamento con Tolbutamida, in Comparation con le Nivellos de Lipoproteina Durante le Therapia a Insulina: Observationes Preliminari

Un augmento significative in le procentage del lipoproteina beta, a base de mesurationes electrophoretic, esseva trovate in 13 patientes post lor transferimento ab insulina a tolbutamida, ben que le sucros esseva regulate non minus ben con tolbutamida in le doses recommendate. Un augmento del lipido ligate

como le fraction globulina beta, amontante a 9 pro cento ± 1,7 (differentia medie), occurreva post un mense de tolbutamida in comparation con le nivellos de controlo sub un regime a insulina in le mesme patientes. Post 6 menses, le augmento amontava a 21 ± 3,41 pro cento. Assi le differentia inter le medias post un e post sex menses esseva 12 ± 4,05 pro cento. Le nivellos de cholesterol manifestava nulle definite tendentia augmentatori o diminutori.

Assi le question se subleva si le stabilisation del stato diabetic esseva de facto adequate in omne aspectos, viste que un redisposition del magnitude describite poteva occurrer in le systema del lipoproteinas. Si o non le redisposition in question affice le degeneration vascular remane a determinar. Studios additional concernite con le lipidos es currentemente in progresso in patientes sub tractamento a tolbutamida. Studios preliminari indica que le totalitate del stato diabetic es stabilisate plus adequatemente con insulina.

# UTILIZATION OF GLUCOSE AND FRUCTOSE IN DIFFERENT DISEASES

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Lowered glucose tolerance was observed in patients suffering from epidemic parotitis (Jacono and Villari[7]) and typhoid fever (Banerjee, Chatterjee and Belavady[2]). No change in glucose tolerance, however, was observed in cholera (Banerjee, Bhadury and Sarkar[1]) although most of the patients had initial hyperglycemia. It has been reported that intravenously administered fructose is better utilized in some pathological conditions than glucose (Weichselbaum, Elman and Lund[12]; Weinstein and Roe[13]). It has been claimed (Root, Stotz and Carpenter[10]; Miller *et al.*[8] and Runyan and Kantor[11]) and questioned (Bannerjee and Divakaran[3,4]) that diabetics utilize fructose better than glucose.

Glucose is administered as a routine procedure to patients suffering from infectious diseases. Fructose might be used in preference to glucose if better utilization could be proven. It was, therefore, of interest to study the effect of intravenously administered glucose and fructose on blood levels of these sugars in patients suffering from smallpox, meningococcal meningitis, tuberculous meningitis, gonorrhea and syphilis and in normal subjects for comparison.

**Methods and Materials.** Patients were mostly young adults. In smallpox cases the effects of injection of sugars were studied the 4th to 6th day of the disease when there were toxic symptoms without subcutaneous edema and secondary infections. In meningococcal and tuberculous meningitis cases, the tests were carried out in acute stages of the disease after diagnosis was confirmed by examination of blood and cerebrospinal fluid. Gonorrhea cases were selected during the acute stage and syphilitic patients were either in secondary or tertiary stages of the disease. Normal subjects were persons admitted to the surgical ward of the hospital for vaginal hydrocele or hernia. Examinations of blood, urine and stool were carried out to ascertain if subjects were otherwise normal. The patients selected were those who were admitted into the hospital without receiving any prior treatment. Tests were carried out before any treatment was given to these patients since treatment itself could modify the sugar response. The patients could not be restudied after suitable convalescence as they had to be discharged earlier to make room for other patients.

Patients and normal subjects from the same economic and social status ate a light dinner in the evening, and next morning before breakfast a fasting sample of venous blood was collected, followed by intravenous injection of 50 ml. of a 25% solution of glucose or fructose. Samples of blood were collected in tubes containing sodium fluoride, at intervals of a half hour, until 2 hours after injection of sugars. Glucose and inorganic P were determined in blood samples collected after injection of glucose. Fructose, true glucose and inorganic P were estimated after injection of fructose. Patients and normal subjects emptied their bladders before and 2 hours after injection of fructose, and fructose eliminated in the urine was estimated.

Total reducing sugars were estimated by the method of Hagedorn and Jensen[6], inorganic P by the method of Fiske and SubbaRow[5], and fructose by the method of Roe[9]. Glucose value was calculated by sub-

tracting the glucose equivalent of fructose from total reducing sugar. It was found that 1 mg. of fructose was equivalent to 1.03 mg. glucose.

**Results.** The results are given in Tables 1 to 3. SMALLPOX. There was initial hyperglycemia but the glucose level fell below the initial value 2 hours after administration of glucose. After fructose injection, the blood level of this sugar was higher than normal in all samples of blood and was still present 2 hours after injection, when normal blood did not show fructose. Inorganic P, which was initially high, decreased slightly after glucose, and more so after fructose.

MENINGOCOCCAL MENINGITIS. The fasting blood glucose level was lower than normal and injected glucose disappeared from the blood at a faster rate than normal. The disappearance of blood fructose was similar to that of normal subjects. The inorganic P of blood after glucose and fructose was similar to that of normal subjects.

TABLE 1.—INITIAL VALUES AND CHANGE IN BLOOD GLUCOSE IN SUBJECTS AFTER INTRAVENOUS INJECTION OF 50 ML. OF 25% GLUCOSE

| *Subjects* | *Fasting blood glucose (mg./100 ml.)* | *Change in blood glucose (mg./100 ml.) hours after injection of glucose* | | | |
|---|---|---|---|---|---|
| | | *½ hour* | *1 hour* | *1½ hour* | *2 hour* |
| Normal (11) | 96 ± 2* | +54 ± 2.6 | +10 ± 2.3 | −6 ± 2.2 | − 2 ± 2.0 |
| Smallpox (24) | 120 ± 2 | +52 ± 1.7 | +16 ± 1.7 | −1 ± 1.4 | −10 ± 1.2 |
| *t* values | 8.51** | 0.62 | 2.09** | 1.89 | 3.40** |
| Meningococcal meningitis (20) | 84 ± 2 | +36 ± 1.6 | +14 ± 1.1 | −3 ± 1.6 | − 8 ±1.3 |
| *t* | 4.24** | 5.81** | 1.56 | 1.09 | 2.46** |
| Tuberculous meningitis (20) | 97 ± 3 | +57 ± 0.8 | +27 ± 1.5 | +7 ± 2.1 | +1 ± 1.6 |
| *t* | 0.27 | 1.43 | 6.16** | 4.25** | 1.16 |
| Gonorrhea (20) | 103 ± 2 | +37 ± 2.0 | +13 ± 1.4 | −4 ± 1.2 | − 5 ± 1.6 |
| *t* | 2.47** | 5.10** | 1.12 | 0.79 | 1.14 |
| Syphilis (20) | 108 ± 2 | +53 ± 0.6 | +23 ± 0.6 | +2 ± 1.3 | − 3 ± 1.5 |
| *t* | 4.24** | 0.36 | 5.47** | 3.07** | 0.39 |

*Mean ± standard error of mean. **These values of *t* are significant at 5% level. Figures in parenthesis indicate number of subjects.

TABLE 2.—INORGANIC PHOSPHORUS VALUES OF BLOOD BEFORE AND AFTER INTRAVENOUS INJECTION OF 50 ML. OF 25% GLUCOSE (MG./100 ML.)

| *Subjects* | *Hours after injection of glucose* | | | | |
|---|---|---|---|---|---|
| | *0 hour* | *½ hour* | *1 hour* | *1½ hour* | *2 hour* |
| Normal (11) | 4.8 ± 0.2 | 4.1 ± 0.2 | 3.7 ± 0.2 | 4.0 ± 0.3 | 4.2 ± 0.2 |
| Smallpox (24) | 6.3 ± 0.2 | 5.9 ± 0.2 | 5.8 ± 0.1 | 6.0 ± 0.1 | 6.3 ± 0.1 |
| Meningococcal meningitis (20) | 4.7 ± 0.1 | 4.2 ± 0.1 | 4.0 ± 0.1 | 4.0 ± 0.1 | 4.0 ± 0.1 |
| Tuberculous meningitis (20) | 4.7 ± 0.2 | 4.3 ± 0.2 | 4.0 ± 0.2 | 4.0 ± 0.2 | 4.2 ± 0.2 |
| Gonorrhea (20) | 5.1 ±0.2 | 4.8 ± 0.2 | 4.7 ± 0.2 | 4.7 ± 0.2 | 4.7 ± 0.2 |
| Syphilis (20) | 6.0 ± 0.2 | 5.7 ± 0.2 | 5.6 ± 0.2 | 5.6 ± 0.2 | 5.6 ± 0.2 |

TUBERCULOUS MENINGITIS. The fasting blood glucose and blood glucose 2 hours after injection of glucose were similar to those of normal subjects. The values 1 and 1½ hour after glucose were significantly higher than normal. Variations in inorganic P levels after glucose were similar to those of normal persons.

GONORRHEA. The fasting blood sugar level was higher, the rise in blood sugar level ½ hour after glucose was less, and values 1, 1½ and 2 hours after glucose were similar to normal subjects. Blood inorganic P which was initially high fell a little after glucose and fructose injections. Fructose was present in the blood 2 hours after injection.

SYPHILIS. The fasting blood glucose level was higher than normal. The initial rise in blood sugar level and blood glucose 2 hours after administration was normal. But the values 1 and 1½ hour after glucose were higher than normal. The rate of disappearance of fructose was slower than normal. Blood inorganic P was initially high and fell slightly after administration of the sugars.

There was a rise in the true glucose level of blood (6 mg. to 13 mg.) after injection of fructose in all patients and normal subjects. Urinary ex-

TABLE 3.—BLOOD LEVELS OF FRUCTOSE, GLUCOSE AND INORGANIC PHOSPHORUS BEFORE AND AFTER INTRAVENOUS INJECTION OF 50 ML. OF 25% FRUCTOSE (MG./100 ML.)

| Subjects | Blood levels of | Hours after injection of fructose 0 | ½ | 1 | 1½ | 2 | Fructose in 24 hour urine (mg.) |
|---|---|---|---|---|---|---|---|
| Normal (12) | F | 0 | 23 ± 1 | 6 ± 1 | 2 ± 0.2 | 0 | 140 ± 7 |
| | G | 99 ± 2 | 112 ± 2 | 102 ± 2 | 91 ± 2 | 99 ± 2 | |
| | IP | 4.6 ± 0.1 | 3.7 ± 0.2 | 3.3 ± 0.2 | 3.4 ± 0.2 | 3.8 ± 0.2 | |
| Smallpox (10) | F | 0 | 35 ± 2 | 12 ± 1 | 3 ± 0.8 | 2 ± 0.6 | 125 ± 11 |
| | G | 124 ± 2 | 133 ± 3 | 127 ± 3 | 122 ± 2 | 116 ± 3 | |
| | IP | 5.7 ± 0.3 | 5.1 ± 0.3 | 4.8 ± 0.2 | 4.7 ± 0.2 | 4.6 ± 0.3 | |
| Meningococcal meningitis (10) | F | 0 | 14 ± 4 | 7 ± 0.5 | 2 ± 0.3 | 1 ± 0.1 | 150 ± 13 |
| | G | 87 ± 2 | 96 ± 2 | 87 ± 2 | 75 ± 2 | 77 ± 1 | |
| | IP | 5.4 ± 0.1 | 4.7 ± 0.2 | 4.1 ± 0.1 | 4.7 ± 0.3 | 4.3 ± 0.3 | |
| Tuberculous meningitis (10) | F | 0 | 25 ± 1 | 11 ± 0.5 | 4 ± 0.3 | 1 ± 0.1 | 145 ± 5 |
| | G | 94 ± 2 | 102 ± 2 | 100 ± 2 | 94 ± 2 | 89 ± 2 | |
| | IP | 4.7 ± 0.2 | 4.2 ± 0.2 | 3.9 ± 0.2 | 4.0 ± 0.2 | 4.5 ± 0.2 | |
| Gonorrhea (10) | F | 0 | 18 ± 1 | 7 ± 0.7 | 2 ± 0.3 | 2 ± 0.2 | 114 ± 4 |
| | G | 98 ± 3 | 104 ± 4 | 98 ± 3 | 91 ± 3 | 89 ± 2 | |
| | IP | 5.0 ± 0.3 | 4.6 ± 0.2 | 4.5 ± 0.2 | 4.5 ± 0.2 | 4.6 ± 0.2 | |
| Syphilis (10) | F | 0 | 33 ± 1 | 16 ± 0.9 | 4 ± 0.3 | 1 ± 0.1 | 141 ± 5 |
| | G | 110 ± 2 | 122 ± 3 | 111 ± 2 | 106 ± 3 | 101 ± 2 | |
| | IP | 5.9 ± 0.3 | 5.5 ± 0.3 | 5.4 ± 0.3 | 5.5 ± 0.3 | 5.6 ± 0.3 | |

Values are mean ± standard error of mean. Figures in parenthesis indicate the number of subjects. F = Fructose, G = Glucose, IP = Inorganic Phosphorus.

cretion of fructose in 2 hours' sample of urine after fructose injection did not vary much from normal in the different patients.

**Discussion.** In all the diseased conditions intravenously injected glucose disappeared from the blood within 2 hours of its administration although initial fasting blood sugar values differed from normal. The blood inorganic P level also diminished after glucose in all the diseases studied. These observations indicate that intravenously administered glucose was utilized by these patients. Injected fructose disappeared from the blood stream at a slower rate than normal in most of the conditions studied. Unlike normal subjects, fructose was found in the blood collected 2 hours after its administration. There was a rise in true glucose content of blood in all patients and normal subjects after intravenous injection of fructose. This might result from conversion of fructose into glucose by hepatic enzymes. Initial blood inorganic P was high in most of the patients studied. This might be due to increased glucose-6-phosphatase activity. Fructose, therefore, was not better utilized by these patients than glucose.

**Summary.** 1. Effects of intravenous injections of glucose and fructose on blood levels of these sugars and on blood inorganic P were studied in patients suffering from smallpox, meningococcal meningitis, tuberculous meningitis, gonorrhea and syphilis and in normal subjects.

2. The rate of disappearance of glucose from the blood in patients suffering from these diseases was similar to that of normal subjects although initial blood sugar values differed from normal. Blood inorganic P, which was initially high in most disease conditions, fell after injection of both glucose and fructose.

3. The rate of disappearance of fructose from the blood was slower in the subjects with disease. The glucose level of the blood rose after injection of fructose in normal and diseased subjects. The urinary excretion of fructose did not differ from normal in the patients investigated.

4. Glucose was well utilized by patients suffering from diseases studied but fructose was not better utilized than glucose, so that fructose has no advantage over glucose in treatment of the diseases.

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## SUMMARIO IN INTERLINGUA

### Le Utilisation de Glucosa e de Fructosa in Varie Morbos

1. Le effecto de injectiones intravenose de glucosa e de fructosa super le nivellos sanguinee de iste sucros e super le concentration sanguinee de phosphoro inorganic esseva studiate in patientes con variola, meningitis meningococcal, meningitis tubercular, gonorrhea, e syphilis e etiam in subjectos normal.

2. Le rapiditate del disparition de glucosa ab le sanguine de patientes suffrente del mentionate morbos esseva simile a illo in le caso de subjectos normal ben que le nivellos initial de sucro sanguinee non esseva le mesmes in le duo gruppos. Le concentration sanguinee de phosphoro inorganic—initialmente alte in le majoritate del conditiones pathologic—declinava post injectiones tanto de glucosa como etiam de fructosa.

3. Le disparition de fructosa ab le sanguine esseva plus lente in le subjectos malade. Le nivello sanguinee de glucosa montava post injectiones de fructosa tanto in subjectos normal como etiam in subjectos malade. Le excretion urinari de fructosa non differeva ab le norma in le casos de patientes investigate.

4. Glucosa esseva ben utilisate per le patientes con le morbos investigate, sed le utilisation de fructosa non esseva melior que illo de glucosa, de maniera que fructosa ha nulle avantage in comparation con glucosa in le tractamento de ille morbos.

## SUMMARIO IN INTERLINGUA

*(See page 732 for original article)*

### Studios Clinic e Metabolic de un Nove Steroide Anabolic, Oxymetholona

Le effectos clinic de un nove steroide synthetic, oxymetholona, esseva studiate in un gruppo de chronicamente malade e mal nutrite patientes. Ganios significative de peso occurreva in approximativemente duo tertios del subjectos con un dosage diurne de 7,5 mg.

Studios metabolic in 2 patientes revelava que retention de nitrogeno occurreva durante periodos de administration de oxymetholona. Augmentos del dosage non pareva exercer ulle effecto additional super le ganio de peso o super le retention de nitrogeno.

Oxymetholona non meliorava le function pulmonar in 3 patientes con sever insufficientia pulmonar secundari a emphysema.

Nulle androgenicitate, nulle retention de natrium o de liquido, e nulle hepatotoxicitate esseva incontrate. Un patiente disveloppava glossodynia durante cata un de duo cursos de oxymetholona.

# CLINICAL AND METABOLIC STUDIES ON A NEW ANABOLIC STEROID, OXYMETHOLONE

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Oxymetholone* is a synthetic steroid designated chemically as 2 hydroxymethylene-17-alpha-methyl-17 beta-hydroxy-3-androstanone. Figure 1 compares the structural formula of oxymetholone with testosterone.

The present study reports the results of administration of oxymetholone to a group of chronically underweight patients, all but one of whom were hospitalized. Metabolic studies were performed on 2 patients and the effect of

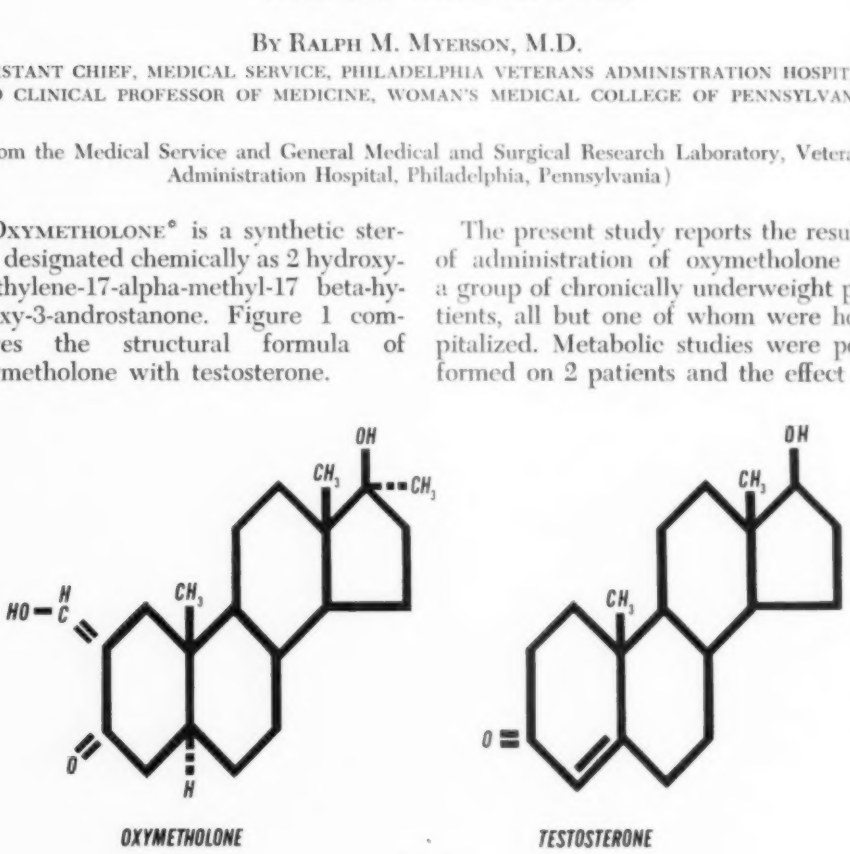


Fig. 1

Previous work indicates that oxymetholone possesses definite anabolic activity (Burke and Liddle[3]). Berkowitz administered oxymetholone to 10 patients with postgastrectomy malnutrition, and utilizing a daily oral dose of 7.5 mg. for a period of 3 months, reported an average weight gain of 8 pounds per patient. No androgenic effects, edema or evidence of hepatic dysfunction were noted[2].

the medication on pulmonary ventilation and blood gases was studied in 3.

**Material and Methods.** Forty-two patients with chronic illnesses associated with weight loss were studied. All patients had been under observation for at least one month prior to the administration of medications and weight charts during this period were available. Many of the patients had had repeated hospitalizations at this institution and the clinical diagnoses were considered established.

*Supplied as Anadrol by Syntex Laboratories, Inc., New York, New York.

Oxymetholone was administered orally to 31 patients in dosage of 7.5 mg. daily (2.5 mg. three times daily) for a period of at least 3 weeks and for as long as 11 months. Thirteen patients were given an inert material for one month; 2 of this group subsequently received oxymetholone. No patient was aware of the nature of the medication prescribed. Diet and other therapies were continued with as little change as possible. All patients were weighed daily and the following laboratory studies were obtained at weekly intervals: hemoglobin, hematocrit, serum alkaline phosphatase, serum cholesterol and serum uric acid. Retention of sulfobromphthalein was measured prior and subsequent to the administration of oxymetholone in most patients. A variety of other laboratory studies were obtained during the period of drug administration depending on the nature of the underlying disease.

One patient on whom nitrogen, phosphorus and calcium balance studies were performed was maintained on a liquid diet containing 2130 calories, 12.7 gm. nitrogen, 1.6 gm. calcium and 1.7 gm. phosphorus daily. Another patient on whom nitrogen excretion alone was determined was on a fixed intake of 11.6 gm. nitrogen daily. Urinary and fecal nitrogen, phosphorus and calcium were determined by standard methods (Fiske and Subbarow[7], Tisdall and Kramer[13]).

The 3 patients on whom serial pulmonary function studies were performed received 15 mg. oxymetholone daily for 3 weeks. Complete ventilatory and blood gas studies were performed by standard methods previously described (Fraimow *et al.*[8]).

**Results.** CLINICAL. Table 1 shows the clinical data on the 31 chronically ill patients who received oxymetholone. Chronic malnutrition was a prominent and refractory symptom in all except patients Nos. 26 and 31 in whom weight loss was modest. Twenty-one of the patients in this group gained 5 pounds or more; the remainder were essentially unchanged. One patient, No. 14, lost 10 pounds. The average weight gain of the entire group was 8.1 pounds, of which 4.1 pounds were gained during the first 4 weeks of therapy.

Table 2 shows the clinical data on 13 chronically ill patients who received an inert compound for 4 weeks. Weight gain was not a prominent feature, in fact, there was an average weight loss of 0.4 pound in the group. The difference in weight gain between the two groups is significant ($P<.01$).

In those patients responding to oxymetholone, weight gain usually began in the first week of therapy although in a few no change was noticed for periods up to 3 weeks. No fixed pattern of the rise in weight could be determined. Those refractory to oxymetholone did not respond to an increase in dosage to 15 mg. daily, and once a plateau was attained in weight gain, increasing the dose to 15 mg. daily did not result in further weight increments. In those patients in whom oxymetholone was discontinued, there was a tendency for a gradual decrease in weight toward original levels. Data, however, are insufficient to evaluate this aspect at present. In patients with malignancies no apparent effect on tumor growth was noticed. Patient No. 12, a 60-year-old white woman, with inoperable carcinoma of the esophagus treated by irradiation, gained 9 pounds in the first 5 weeks of oxymetholone administration, but despite continuation of the medication, returned to her original weight in the subsequent 9 weeks due to the inexorable course of her disease. Patient No. 29, a 43-year-old white man with multiple sclerosis, is of interest since he has been receiving oxymetholone for 11 months. He had been known to this institution for 7 years during which time his weight had never been above 105 pounds, although his average weight prior to his illness had been 140 pounds. During the first 8 weeks of oxymetholone therapy he gained 12 pounds but despite continuation of the drug for 9 more months, including doses of 15 mg. per day, no further weight gain has occurred.

Some patients have commented on

TABLE 1.—CLINICAL DATA ON PATIENTS RECEIVING OXYMETHOLONE

| *Pt.* | *Age* | *Sex* | *Diagnosis* | *Wgt. Loss During Disease (lbs.)* | *Wgt. Before Oxymetholone (lbs.)* | *Duration of Medication (weeks)* | *Wgt. After Oxymetholone (lbs.)* | *Net Change (lbs.)* | |
|---|---|---|---|---|---|---|---|---|---|
| 1. | 62 | M | Pulmonary Emphysema | 15 | 116 | 10 | 137 | +21 | |
| 2. | 61 | M | " | 30 | 111 | 4 | 122 | +11 | |
| 3. | 73 | M | " | 30 | 109 | 9 | 120 | +11 | |
| 4. | 66 | M | " | 34 | 66 | 6 | 74 | + 8 | |
| 5. | 73 | M | " | 20 | 100 | 6 | 105 | + 5 | |
| 6. | 64 | M | " | 40 | 85 | 15 | 91 | + 6 | |
| 7. | 63 | M | " | 30 | 118 | 3 | 118 | 0 | |
| 8. | 63 | M | Bronchogenic Ca | 30 | 115 | 5 | 130 | +15 | |
| 9. | 62 | M | Bronchogenic Ca | 50 | 112 | 3 | 121 | + 9 | |
| 10. | 63 | M | " | 35 | 108 | 3 | 105 | − 3 | |
| 11. | 68 | M | Esophageal Carcinoma | 50 | 70 | 7 | 86 | +16 | |
| 12. | 60 | F | " | 20 | 115 | 5 | 114 | + 9 | (see text) |
| 13. | 46 | M | Hodgkin's Disease | 25 | 129 | 3 | 139 | +10 | |
| 14. | 64 | M | " | 30 | 120 | 3 | 110 | −10 | |
| 15. | 22 | M | Lymphoepithelioma with Metastases | 35 | 93 | 3 | 101 | + 8 | |
| 16. | 69 | M | CA of Colon with Metastases | 40 | 100 | 6 | 116 | +16 | |
| 17. | 68 | M | Chr. Lymph. Leukemia | 40 | 125 | 3 | 134 | + 9 | |
| 18. | 27 | M | Chr. Ulcerative Colitis | 60 | 105 | 18 | 133 | +28 | |
| 19. | 26 | M | " | 60 | 106 | 7 | 127 | +21 | |
| 20. | 31 | M | " | 85 | 89 | 4 | 89 | 0 | |
| 21. | 62 | M | Chr. Pancreatitis with Insufficiency | 50 | 112 | 4 | 126 | +14 | |
| 22. | 42 | F | Malabsorption Syndrome | 75 | 97 | 5 | 97 | 0 | |
| 23. | 66 | M | Generalized Arteriosclerosis | 40 | 110 | 5 | 110 | 0 | |
| 24. | 70 | M | " | 40 | 96 | 11 | 99 | + 3 | |
| 25. | 77 | M | " | 15 | 135 | 7 | 142 | + 7 | |
| 26. | 70 | M | Exfoliative Dermatitis | −12 | 138 | 3 | 143 | + 5 | |
| 27. | 42 | M | " | 40 | 115 | 6 | 115 | 0 | |
| 28. | 64 | M | Rheumatoid Arthritis | 35 | 105 | 3 | 105 | 0 | |
| 29. | 43 | M | Multiple Sclerosis | 35 | 102 | 48 | 114 | +12 | (see text) |
| 30. | 42 | M | Sarcoidosis | 30 | 125 | 4 | 130 | + 5 | |
| 31. | 34 | M | Gout | 10 | 140 | 3 | 139 | − 1 | |

improvement in well-being and appetite while receiving oxymetholone. No evidence of androgenicity or edema has been noticed. Mercurial diuretics were administered to those patients in whom salt and fluid retention were considered a possibility (patients Nos. 1 to 6, 8, 17, 25) and no significant diuresis occurred. Determinations of total body water content were not done. No change in any laboratory tests including studies of liver function have been noted. The only possible side effect occurred in patient No. 22, a 42-year-old woman with idiopathic malabsorption syndrome who complained of severe sore tongue following 4 weeks of oxymetholone therapy. Despite high doses of parenteral vitamins, cheilosis and glossitis had been a persistent finding in this patient for many months but had not been a source of subjective complaints up until this time. Oxymetholone was discontinued and the glossodynia disappeared without any improvement in the appearance of the tongue. Reinstitution of oxymetholone 2 weeks later was followed by a prompt return of glossodynia.

METABOLIC STUDIES. The effect of oxymetholone on urinary nitrogen excretion was studied in one patient. The patient was on a regulated, steady intake of 11.6 gm. of nitrogen daily during the periods of both control and drug administration.

During the period when oxymetholone was being administered in a dosage of 5 mg. daily, retention of nitrogen occurred. During the second control period there was a prompt return to nitrogen excretion levels approximating those that existed during the first control period (Table 3).

Another patient was studied in an attempt to determine the effects of increasing dosages of oxymetholone. Urinary and fecal excretion of nitrogen, phosphorus and calcium were determined during administration of 10 mg., 20 mg., and 30 mg., of oxymetholone daily. Drug administration at each dosage level was preceded by a control

TABLE 2.—WEIGHT CHANGES IN PATIENTS RECEIVING INERT MATERIAL FOR A PERIOD OF 4 WEEKS

| *Pt.* | *Age* | *Sex* | *Diagnosis* | *Wgt. Loss During Illness (lbs.)* | *Weight Before Inert Material (lbs.)* | *Weight After Inert Material (lbs.)* | *Net Change* |
|---|---|---|---|---|---|---|---|
| 4. | 66 | M | Pulmonary Emphysema | 34 | 68 | 66 | − 2 |
| 20. | 31 | M | Chronic Ulcerative Colitis | 85 | 89 | 89 | 0 |
| 32. | 62 | M | Multiple Burns | 35 | 110 | 110 | 0 |
| 33. | 69 | M | Generalized Arteriosclerosis | 25 | 138 | 136 | − 2 |
| 34. | 63 | M | " | 30 | 112 | 113 | + 1 |
| 35. | 69 | M | " | 15 | 152 | 157 | + 5 |
| 36. | 64 | M | Pulmonary Emphysema | 40 | 107 | 108 | + 1 |
| 37. | 42 | F | Pulmonary Tuberculosis | 20 | 133 | 133 | 0 |
| 38. | 53 | M | Bronchogenic Carcinoma | 25 | 160 | 150 | −10 |
| 39. | 38 | M | Convalescent Gullain-Barre Syndrome | 25 | 160 | 158 | − 2 |
| 40. | 40 | M | " | 20 | 155 | 158 | + 3 |
| 41. | 67 | M | Exfoliative Dermatitis | 40 | 102 | 102 | 0 |
| 42. | 50 | M | Rheumatic Heart Disease | 45 | 94 | 95 | + 1 |

period during which the patient was on diet alone and received no medication. The results of this study are shown in Table 4.

It will be noted that the greatest retention of nitrogen occurred during the first period and when the patient was receiving 10 mg. of oxymetholone. Calcium and phosphorus retention also occurred during this period. During subsequent courses of 20 mg. and 30 mg. of oxymetholone, nitrogen retention was essentially unchanged and there appeared to be no effect in phosphorus and calcium.

PULMONARY FUNCTION. Three patients with severe pulmonary insufficiency due to emphysema were studied before and after a 3-week course of oxymetholone in dosage of 15 mg. daily. No significant changes were noted. Patient No. 3 experienced a drop in arterial plasma $CO_2$ from 77.5 to 69.7 volumes %. Further studies are being done to determine the possible significance of this isolated change.

**Discussion.** Although the anabolic activity of testosterone and related steroids has been well established (Drill and Saunders[6], Kochakian[10]), their use is often limited by side effects. These are usually androgenic in nature, but retention of sodium and water may be a serious problem especially in the elderly. Liver damage of a cholestatic type has also been reported with some testosterone derivatives (Almaden and Ross[1], Kory *et al.*[11], Schaffner, Popper and Chesrow[12], Werner, Hanger and Kritzler[15]).

Many compounds have been synthesized and studied in an attempt to decrease androgenic activity while at the same time retaining or increasing anabolic potency. The present observations indicate that oxymetholone is an effective anabolic agent at a dose of 7.5 mg. daily. Significant weight gain was experienced by approximately two-thirds of patients receiving oxymetholone and there was a subjective improvement in appetite and well-being.

TABLE 3.—URINARY NITROGEN DATA IN PATIENT RECEIVING 5 MG. OXYMETHOLONE DAILY

| *Regimen* | *Duration (days)* | *Urinary N mg./day ± SD* |
|---|---|---|
| Control (Diet Alone) | 22 | 4,276 ± 317 |
| 5 mg. Oxymetholone/Day | 29 | 3,608 ± 280 |
| Control (Diet Alone) | 20 | 4,350 ± 330 |

TABLE 4.—EFFECTS OF INCREASING DOSAGES OF OXYMETHOLONE ON TOTAL (URINARY AND FECAL) EXCRETION OF NITROGEN, PHOSPHORUS AND CALCIUM

| *Regimen* | *Duration (days)* | *Excretion (gm./day)* | | |
|---|---|---|---|---|
| | | *N* | *P* | *Ca* |
| Control | 6 | 10.6 | .76 | .56 |
| 10 mg. Oxymetholone/Day | 9 | 6.6 | .62 | .28 |
| Control | 6 | 11.2 | .89 | .69 |
| 20 mg. Oxymetholone/Day | 10 | 8.9 | .90 | .79 |
| Control | 6 | 10.1 | .80 | .78 |
| 30 mg. Oxymetholone/Day | 7 | 8.9 | .83 | .80 |

TABLE 5—RESULTS OF PULMONARY FUNCTION STUDIES ON 3 PATIENTS BEFORE AND AFTER OXYMETHOLONE

| | | *Patient No. 1* | | *Patient No. 3* | | *Patient No. 6* | |
|---|---|---|---|---|---|---|---|
| | *Normal* | *8-24-60 Before Oxymetholone* | *9-13-60 After Oxymetholone* | *8-25-60 Before Oxymetholone* | *9-13-60 After Oxymetholone* | *8-22-60 Before Oxymetholone* | *9-13-60 After Oxymetholone* |
| Vital Capacity (% Normal) | >80% | 92 | 89 | 82 | 71 | 69 | 63 |
| 3″ V.C. (%) | >90% | 69 | 71 | 54 | 53 | 62 | 72 |
| Max. Br. Cap. (% Normal) | >80% | 60 | 62 | 38 | 27 | 37 | 26 |
| Min. Vent. ($L/M^2$ BSA) | 3–4 | 4.52 | 4.58 | 3.22 | 4.47 | 3.22 | 4.02 |
| $O_2$ Uptake ($ml./M^2/Min.$) | 120–140 | 102 | 113 | 138 | 144 | 121 | 125 |
| R.Q. | .75–.95 | .77 | .75 | .75 | .70 | .89 | .74 |
| B.M.R. | −10 to +10 | −20 | −10 | +7 | +12 | −3 | −2 |
| Phys. Dead Space (ml.) | 140–160 | 209 | 264 | 198 | 226 | 193 | 240 |
| Art. $O_2$ Sat. (%) | >92% | 85.2 | 83.2 | 77.0 | 79.8 | 89.2 | 87.8 |
| Art. Plasma $CO_2$ (Vol. %) | 55–60 | 64.4 | 66.9 | 77.5 | 69.7 | 60.1 | 64.3 |
| Art. pH | 7.37–7.42 | 7.38 | 7.38 | 7.37 | 7.39 | 7.38 | 7.38 |
| Art. $CO_2$ Tension (mm. Hg) | 38–42 | 48 | 50 | 59 | 51 | 45 | 48 |

No evidence of androgenicity, salt or fluid retention or hepatotoxicity was encountered.

Nitrogen balance studies in 2 patients revealed an increase in nitrogen retention during oxymetholone administration. No increase in nitrogen retention occurred when the dose of oxymetholone was doubled or trebled.

Retention of phosphorus and calcium occurred on dosage of 10 mg. of oxymetholone, but at 20 mg. and 30 mg. dosages there were no significant differences from control periods. Further studies are being done to determine whether this is a constant finding.

The reports of the beneficial effects of progesterone in severe pulmonary emphysema, prompted a trial of oxymetholone in this disease (Cullen, Brum and Reidt[4], Döring, Loeschcke and Ochwadt[5], Goodland *et al.*[9]). Tyler has reported no improvement in pulmonary function with a small group of steroid compounds closely related to progesterone[14].

**Summary.** The clinical effects of a new synthetic steroid, oxymetholone, were studied in a group of chronically ill, malnourished patients. Significant weight gain occurred in approximately two-thirds of the patients on a dosage of 7.5 mg. daily.

Metabolic studies on 2 patients revealed that nitrogen retention occurred during periods of oxymetholone administration. Increasing dosages appeared to have no further effect either on weight gain or nitrogen retention.

Oxymetholone did not improve pulmonary function in 3 patients with severe pulmonary insufficiency secondary to emphysema.

No androgenicity, sodium or fluid retention or hepatotoxicity was encountered. One patient developed glossodynia during each of two courses of oxymetholone.

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*(Interlingua on page 731)*

# LISTERIOSIS: REPORT OF 5 CASES

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Murray, Webb and Swann[8] described a disease of rabbits characterized by a large mononuclear leukocytosis and caused by a small Gram-positive non-sporing bacillus, which they called *Bacterium monocytogenes*. The same organism has since been isolated by a number of workers from various diseases in animals and man. Pirie[10] proposed the generic name of Listerella for this organism, but since this name had previously been used for a mycetozoan, he later suggested the name Listeria[11].

The organism is a Gram-positive bacillus which morphologically resembles members of the Corynebacterium genus. The colonies usually produce a zone of beta hemolysis on a blood agar plate. The organism is very sluggishly motile. The motility is best demonstrated by growth in a semi-solid medium at 25° C. Flagella are developed better at 25° C. than at 37° C. (Griffin and Robbins[2]). Tentative identification can be made by growth characteristics, morphology and motility. Identification may be verified by serologic testing with H and O antisera, but these antisera are not readily available. Virulence can be demonstrated by inoculation into laboratory animals. Subcutaneous or intraperitoneal inoculation of liquid cultures of the organism into mice causes death in one to 4 days. Intravenous inoculation in the rabbit proves fatal in 24 hours. Instillation of a pure culture into the conjunctival sac of a rabbit gives rise to a severe conjunctivitis within 24 hours followed by keratitis.

Seeliger[12] listed 298 human infections due to Listeria in 1955. The number of cases reported has increased each year, especially since 1952. There are several recent reviews on this subject (Dedrick[1], Murray[7], Hoeprich[4], Hood[5], Seeliger[12]).

Listeria produces a variety of types of infections in man. The organism may cause a septic infection closely resembling infectious mononucleosis, but it most frequently produces a meningitis or encephalitis or both. One

form of the infection resembles typhoid fever. Granulomatous sepsis in the newborn occurs while the mother has only a very mild infection. There is also an oculoglandular infection due to Listeria. There has been only one case reported of bacterial endocarditis due to Listeria (Hoeprich and Chernoff[3]). Jordon and Thomas[6] reported growing Listeria in repeated blood cultures from a man with a presumed congenital heart disease. Insufficient clinical data were presented to make a diagnosis of bacterial endocarditis but their patient expired after what may have been cerebral embolization. Necropsy was not permitted. Since September, 1957, we have observed 5 infections due to Listeria at the University of Oklahoma Medical Center. Two of these were bacterial endocarditis.

**Case Reports. Meningitis.** CASE 1. A.L. was a 63-year-old white farmer who had a subtotal gastric resection for gastric ulcer. He was admitted to the hospital one year later with a marked anemia which proved to be on a hemolytic basis. He failed to respond to splenectomy, but did have modest improvement in his anemia while on large doses of prednisone. He later developed fever, prostration, and nuchal rigidity over a 24-hour period. Examination of cerebrospinal fluid showed 3,200 leukocytes per c.mm. with 90% neutrophils. Cultures of this fluid showed growth of *Listeria monocytogenes*. The acute symptoms were alleviated after treatment with penicillin, streptomycin, and tetracycline. He later developed numerous monilial lesions of the mouth and tongue. He died one month after the onset of the Listeria meningitis of a septicemia due to Proteus. Permission for necropsy was denied.

CASE 2. J.F.A. was a 68-year-old white man who was hospitalized 6 months prior to his final admission. A cholecystectomy was performed at that time. He was found to have a cobblestone liver at surgery and subsequent liver function studies supported the diagnosis of cirrhosis. He was readmitted because of edema and anorexia. The liver was markedly enlarged. Abdominal distension increased while he was in the hospital and he failed to respond to diuretics. He developed confusion and asterixis (flapping tremor) and was given potassium glutamate and oral neomycin. On the twenty-first hospital day, he developed fever and nuchal rigidity. The cerebrospinal fluid contained 4,000 white cells per c.mm. with 57% lymphocytes and 43% neutrophils. *L. monocytogenes* was cultured from this fluid. He was treated with chloramphenicol, streptomycin and penicillin. He expired less than 24 hours after the onset of the meningeal symptoms. Necropsy disclosed that he had acute purulent meningitis and portal cirrhosis. He was also found to have a primary carcinoma of the liver, liver cell type, with invasion of the portal vein, hepatic veins, inferior vena cava and the left renal vein.

**Septicemia.** CASE 3. B.B.S. was an infant who was born in the hospital. The mother was apparently in good health. The pregnancy and the delivery were uncomplicated. The cord had been treated prophylactically with chlortetracycline ointment. The following day he had a purulent conjunctivitis with a temperature of 100° F. The child was thin, fed poorly, and had a weak cry. The following day the temperature was 102° F. and an erythematous, macular rash was present. The right lung was consolidated. Treatment with intramuscular chloramphenicol failed to alter the clincal course and the child expired 3 days after birth. Cultures of the conjunctivae, blood, and stool revealed *Listeria monocytogenes*. Vaginal culture from the mother did not grow Listeria, and she was never clinically ill.

**Bacterial Endocarditis.** CASE 4. K.M. was a 28-year-old white male farmer who had two episodes of fever and arthralgia typical of rheumatic fever when he was 10 and 13 years of age. He had no further difficulties until he was admitted to the hospital with dyspnea, edema, cardiomegaly, and abdominal discomfort. It was noted that he had a fever, systolic and diastolic murmurs at both the base and apex of the heart, and intermittent hematuria. There were a few petechiae on one conjunctiva. *Listeria monocytogenes* was isolated from several blood cultures. He was treated with penicillin and streptomycin with improvement. He developed atrial fibrillation which was followed by a sudden right hemiplegia. Quinidine converted his rhythm to normal and he was given bishydroxycoumarin for the remainder of his hospital course, which was thereafter unremarkable.

CASE 5. E.S. was a 55-year-old alcoholic male who was first admitted to the hospital in February, 1958, with acute abdominal pain and vomiting. The serum amylase was 320 units per ml. and he was thought to have gastritis and pancreatitis. He was next ad-

mitted in July of the same year with similar symptoms. The serum amylase was then 6,500 units per ml. He developed jaundice and a mass became palpable in the left upper quadrant. Subsequently, at laparotomy a large pancreatic cyst was found. He had a choledochoduodenostomy and cystojejunostomy. He improved and left the hospital, but returned to the hospital on January 15, in a state of marked dehydration and confusion and died within a few hours. A necropsy was done. There was acute dilatation of the left heart and pulmonary edema as well as carcinoma of the head of the pancreas with liver metastases. There were recent vegetations on the mitral valve with destruction of the posterior leaflet. Culture of the vegetations revealed *Listeria monocytogenes*.

BACTERIOLOGIC STUDIES. The organisms isolated from these cases were consistent in their cultural characteristics and their biochemical reactions. They were found to be non-motile at 37° C., but sluggishly motile at room temperature in a semi-solid medium. On blood agar, the colonies appeared smooth, translucent, and were about 1 mm. in diameter. Hemolysis occurred when blood agar plates were incubated at 37° C. for 3 or 4 days. No hemolysis was observed on blood agar when incubated less than 24 hours. Most strains grew well on ordinary diagnostic media. Growth occurred equally well in the presence of atmospheric oxygen or under reduced oxygen tension. The biochemical reactions were relatively inactive. Acid, but no gas, was produced in glucose, sucrose, salicin, maltose and mannitol. Citrate was not utilized, urea was not decomposed and indol was not formed. The organisms gave a positive methyl red and acetylmethylcarbinol reaction.

Each strain isolated was grown in a broth culture for 24 hours and then 0.4 ml. of the culture was inoculated intraperitoneally into white mice. Death of the animals occurred between 24 and 48 hours. Organisms were isolated from the spleen, liver and heart of the animals upon necropsy.

The drug susceptibilities of the organisms isolated in each case were similar. All isolates tested were susceptible to penicillin, streptomycin, chloramphenicol and tetracyclines by the disk method.

**Discussion.** There are two features of *Listeria monocytogenes* which tend to mislead the bacteriologist in identifying the organism. First, its cellular morphology is identical with diphtheroids found in the normal flora of the skin and throat, and second, the colonies on blood agar closely resemble streptococcal colonies. Both of these features have been stressed by writers on the subject as pitfalls in identification. Listeria can be differentiated from diphtheroids by several means. Testing for motility at 25° C. and at 37° C. is probably the quickest and easiest method. Animal virulence testing can be done using the rabbit's eye inoculation or by intraperitoneal inoculation of the mouse. The fermentation reactions are highly suggestive of the true identification. Finally, the serological tests are accurate in identification, but require considerable time. They are performed at the U.S. Public Health Service Communicable Disease Center. In short, the identification is not difficult but is dependent on alertness leading to further testing of suspected colonies by the bacteriologist.

There are no special features of the illness to make the physician suspicious of the presence of listeriosis. The organism causes a variety of clinical syndromes that can be produced by a number of other bacteria. In the list given earlier of various infections that have been found to be due to *Listeria monocytogenes*, it will be noted that none of these diseases is peculiar only to Listeria. Our cases, if the infant be excluded, were all ill with another disease. In these cases, it appears that Listeria was an opportunist and that

it was not necessary for it to possess a high degree of pathogenicity.

The clinical picture of Listeria meningitis has been reported most often. Any bacterium that is isolated from a case of purulent meningitis is assumed to be the pathogen, and virulence is seldom questioned or tested. This assumption does not apply, however, in several other instances of bacteria isolated by routine culturing. For example, when a diphtheroid is found in a throat culture, a motility test and other identifying studies are usually not performed. Several authors have suggested that cultures of Listeria are often discarded without their true nature being suspected. If this be true, there should be a relatively large group of either subclinical or mild, inapparent infections with this organism. The occurrence of such cases would explain many of the puzzling aspects of the epidemiology of listeriosis. The occurrence of such inapparent infections was suggested by Osebold and Sawyer[9], who found agglutinating antibodies to *Listeria monocytogenes* in the sera of 77 of 468 veterinarians.

The solutions to the above problems await further investigative work. A search for the organism should be carried out in both healthy people and in patients with various mild but nonspecific illnesses. A simple screening test comparable in ease and accuracy to the skin tests used in tuberculosis and fungal diseases would be highly desirable in such a study. And, of course, more suspicion on the part of both physicians and bacteriologists should turn up more data on the pattern of infection.

**Summary.** Five cases of listeriosis have been recognized in this medical center in 2½ years. The infections found were 2 cases of meningitis, 2 cases of bacterial endocarditis, and one case of infant septicemia. Of the 4 affected adults, 3 were debilitated due to other diseases and one had rheumatic valvular heart disease. Although there are many reports of Listeria meningitis and infant septicemia, there has been only one other case of bacterial endocarditis due to Listeria reported. The diagnosis of Listeria infection is usually made in the bacteriology laboratory, and is rarely suspected clinically. The organisms are Gram-positive rods resembling diphtheroids, and can easily be discarded as a contaminant or as normal flora. The organisms are motile, and motility studies, if done, furnish the best clue as to their correct identification.

In this series, Listeria appeared to be an opportunist, and it is suggested that many inapparent infections occur. More awareness of the problem by the routine clinical bacteriology laboratory is necessary to extend our limited knowledge of the epidemiology of listeriosis in man. Elucidation of the puzzling aspects of the epidemiology of listeriosis in man will depend upon recognition of *Listeria monocytogenes* in routine bacteriologic cultures.

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## SUMMARIO IN INTERLINGUA

### Listeriosis: Reporto de Cinque Casos

A iste centro medical, cinque casos de listeriosis esseva recognoscite in le curso de duo annos e medie. Le infectiones trovate esseva 2 casos de meningitis, 2 de endocarditis bacterial, e 1 de septicemia infantil. Inter le quatro afficite adultos, tres esseva debilificate per altere morbos, e un habeva morbo rheumatic de valvula cardiac. Ben que il existe multe reportos de meningitis e de septicemia infantil a causation per listeria, solmente un previe reporto esseva trovate de endocarditis bacterial con listeria como organismo incriminate. Le diagnose de infection per listeria es facite usualmente in le laboratorio bacteriologic. Illo es suspicite rarmente a bases clinic. Le organismos es bastonettos Gram-positive e resimila diphtheroides. Il es facile discartar los como contaminantes o elementos del flora normal. Illos es motil, e studios de motilitate (si effectuate) provide le melior clave pro lor identification correcte.

In le presente serie, listeria esseva apparentemente un opportunista. Il es a supponer que multe inapparente infectiones per listeria occurre. Il es necessari que le laboratorio bacteriologic clinic se interessa in su routine plus consciemente in iste problema, si nos vole extender nostre nunc restringite cognoscentias del epidemiologia de listeriosis in le homine. Le elucidation del aspectos mystificante del epidemiologia de listeriosis in le homine depende del recognition de *Listeria monocytogenes* in routinari studios de culturation bacteriologic.

## SUMMARIO IN INTERLINGUA

*(See page 744 for original article)*

### Le Effecto de Mustarda de Nitrogeno Super le Function Adrenal

Es describite un studio quantitative del effecto de $HN_2$ super le axe hypothalamico-pituitario-adrenal in un casuistica de 9 patientes. Le typo e le grado del responsa esseva variabile. Mustarda de nitrogeno induce, il es ver, le liberation de ACTH in certe casos, sed illo non promove le capacitate del pituitario de responder post iste typo de stress. Le responsa pituitari o adrenal (o ambes) es deprimite durante le therapia a $HN_2$ in certe patientes. Le responsa pituitari a SU 4885 non reflecte necessarimente le capacitate del pituitario de responder al stress de $HN_2$. Es discutite le mechanismo del liberation de ACTH per le pituitario como resultato del stress per $HN_2$.

# THE EFFECT OF NITROGEN MUSTARD ON ADRENAL FUNCTION*†

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Nitrogen mustard ($HN_2$) is used in the treatment of pathological tissue and vascular reactivity, withdrawal syndromes from exogenous steroids and neoplasms (Scherbel[29], Scherbel, Schuchter and Harrison[30], Zubrod[35]). The effectiveness of $HN_2$ in the treatment of these entities suggests its mode of action may be due in part to a stimulatory effect on the hypothalamic-pituitary-adrenal axis. The purpose of this investigation is to report a quantitative study of the effect of $HN_2$ as a stressor agent on the function and responsiveness of the hypothalamic-pituitary-adrenal axis.

Most evidence for the mode of action of nitrogen mustard points to an intramolecular transformation in the cell with the release of chloride ion and the formation of the highly reactive ethylenimonium derivative (Goodman and Gilman[10]). The efficacy of $HN_2$ in the treatment of neoplasms and diseases of the reticuloendothelial system is related to its ability to inhibit the resting phase of the mitotic cycle (Gilman and Philips[7]). Nitrogen mustard possesses a high degree of reactivity with specific nucleoproteins that are essential to nuclear reproduction (Goldthwait[9], Scherbel[29]). An example of the drug's effect on vascular reactivity is the inhibition of the Schwartzman phenomenon; it is postulated that this occurs by a systemic effect rather than by rendering the vascular endothelial cells anergic (Becker[2], Scherbel[29], Schlang[31,32], Wissler, Fitch and LaVia[34]). Injection of rats with $\beta$-chlorethyl vesicants stimulates adrenocortical activity as measured by adrenal hypertrophy, decreased adrenal ascorbic acid, decreased adrenal cholesterol and decreased adrenal lipids (Ludewig and Chanutin[21,22]). $HN_2$ given to adrenalectomized rats causes an increased toxic effect as does any other form of stress (that is, pain, cold, burns) (Karnofsky, Graef and Smith[15]).

The response of the hypothalamic-pituitary-adrenal system is evaluated experimentally by determining such parameters as adrenal weight, adrenal ascorbic acid, adrenal cholesterol, bioassay of pituitary tissue, circulating lymphocytes and circulating eosinophils (Holub, Kitay and Jailer[12,16], Royce and Sayers[27], Sayers[28]). The introduction of 2-methyl-1, 2 bis-(3 pyridyl)-1-propanone (SU 4885) has afforded a means of indirectly estimating pituitary ACTH secretion (Gold, DiRaimondo and Forsham[8], Jenkins *et al.*[14], Liddle *et al.*[20]). This compound, in low doses, inhibits 11$\beta$-hydroxyla-

TABLE 1.—24-HOUR URINARY 17-KETOGENIC STEROIDS DURING SU-4885, ACTH AND $HN_2$ EXPRESSED AS FRACTION OF THE BASELINE VALUE OF 1.00

*Supported by U.S.P.H. S.-Grant No. A-504.
†Su 4885 kindly supplied by C. H. Sullivan, M.D., Ciba Pharmaceutical Products, Inc.

TABLE 1.—24-HOUR URINARY 17-KETOGENIC STEROIDS DURING SU-4885, ACTH AND $HN_2$ EXPRESSED AS FRACTION OF THE BASELINE VALUE OF 1.00

| | *Before $HN_2$* | | *During $HN_2$* | | | | *After $HN_2$* | | |
|---|---|---|---|---|---|---|---|---|---|
| *Patient* | *SU-4885 Response* | *ACTH Response* | *1st Day* | *2nd Day* | *3rd Day* | *4th Day* | *SU-4885 Response* | *ACTH Response* | *Comment* |
| 1. A.R. | 0.75 | 0.87 | 0.37 | 0.13 | 0.68 | 0.84 | 0.68 | 0.48 | 38 yr. old Caucasian female. Dx: Rheumatoid arthritis Exogenous corticosteroids stopped 3 yrs. prior to study. |
| 2. H.Y. | 1.88 | 1.35 | 16.50 | 7.50 | 2.50 | 1.60 | 3.14 | 2.88 | 44 yr. old Caucasian male. Dx: Dermatomyositis. No history of steroids. |
| 3. E.K. | 3.71 | 3.27 | 0.32 | 0.07 | 0.92 | 1.39 | 2.61 | 3.43 | 31 yr. old Caucasian female. Dx: Bronchial asthma. Heavy doses of corticosteroids; stopped 9 days prior to study. |
| 4. F.M. | 1.89 | 3.52 | 2.81 | 3.24 | | | 1.54 | 2.16 | 69 yr. old Caucasian female. Dx: Hodgkin's granuloma. No history of corticosteroids. |
| 5. J.K. | | | 0.88 | 0.48 | 0.67 | | | 1.75 | 65 yr. old Caucasian male. Dx: Carcinoma of lung. No history of corticosteroids. |
| 6. H.A. | 1.61 | 2.96 | 3.12 | 1.54 | | | 1.42 | 2.78 | 35 yr. old Caucasian female. Dx: Hodgkin's granuloma. No history of corticosteroids. |
| 7. M.F. | 1.82 | 1.67 | 1.24 | 0.80 | 1.10 | | 1.06 | 1.23 | 67 yr. old Caucasian female. Dx: Lupus erythematosus. Intermittant corticosteroids for 6 months prior to study. |
| 8. V.R. | 0.81 | 1.38 | 1.40 | 1.34 | | | 0.74 | 0.75 | 38 yr. old Caucasian male. Dx: Hodgkin's granuloma. 40 mg. hydrocortisone daily until 3 weeks prior to study. Hypoadrenal withdrawal syndrome 1 week prior to study. |
| 9. C.S. | | | 1.86 | 1.44 | 2.25 | | | 6.49 | 75 yr. old Caucasian male. Dx: Carcinoma of lung. No history of corticosteroids. |

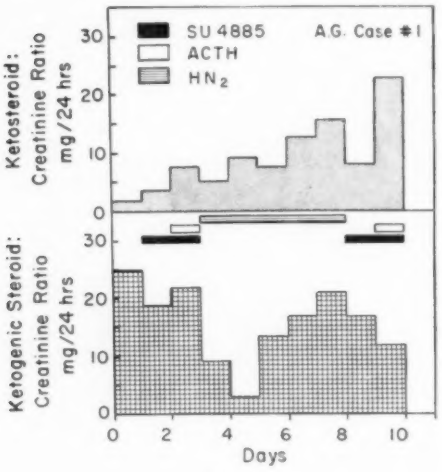


Fig. 1

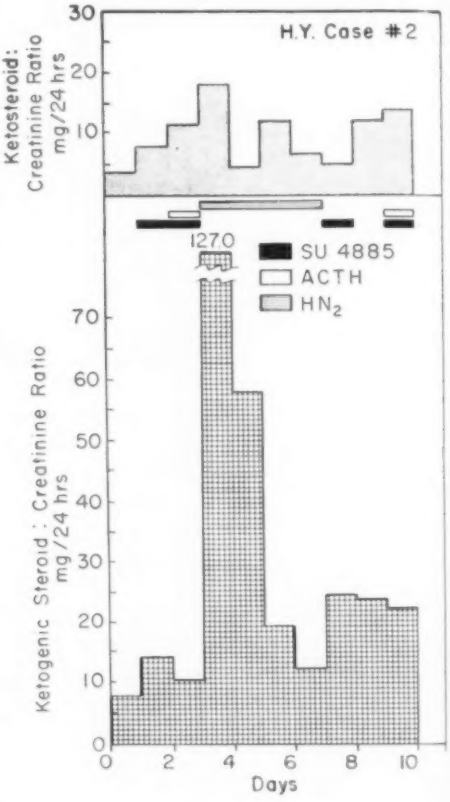


Fig. 2

tion of the cyclopentanoperhydrophenanthrene ring. Thus the formation of hydrocortisone is inhibited, and the feedback mechanism for control of pituitary ACTH release is blocked. The release of endogenous ACTH may then be followed indirectly by measuring 24-hour urinary excretion of 17-ketogenic steroid (17-KGS) and 17-ketosteroid (17-KS). The primary adrenal steroid excretion product, after SU 4885 administration, is tetrahydro-11-desoxycortisol. Minimal inhibition of pituitary ACTH release is ascribed to 11-desoxycortisol.

**Methods and Materials.** Selected patients, age 31 to 75, were removed from all exogenous adrenocortical steroids and daily 24-hour urine collections were obtained. Urinary 17-KGS (modified Norymberski method) (Sobel *et al.*[33]) and 17-KS (Drekter *et al.*[6]) were determined for each 24-hour collection. After baseline studies were obtained, each patient was given SU 4885 (30 mg. per kg., body weight) in 1000 ml. normal saline intravenously over an 8-hour period. The following day the SU 4885 was repeated with the addition of 25 units of aqueous ACTH. On subsequent days, divided doses of $HN_2$ were given intravenously; the total dose ranged from 0.2 mg. per kg. body weight to 0.4 mg. per kg.. Following completion of the nitrogen mustard therapy, intravenous SU 4885 and SU 4885 plus ACTH were repeated (as noted above). Creatinine was determined for each 24-hour urine volume and urine steroids were corrected to 1 gm. of creatinine excretion per 24 hours for purposes of comparison.

**Results.** The urinary KGS responses to SU 4885, ACTH and $HN_2$ have been compared to the baseline urinary KGS obtained at the beginning of the study (Table 1). The urinary KS response parallels that of KGS but is a less sensitive indicator of adrenocortical function (Figs. 1–9).

SU 4885 STIMULATION. The urinary 17-KGS, after a prestress challenge with SU 4885, were low in Cases 1 and 8. This could be a manifestation of

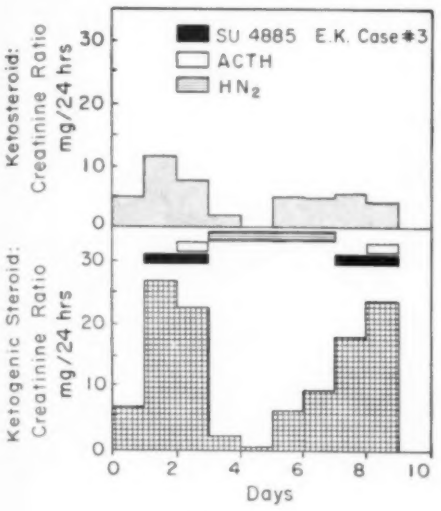


Fig. 3

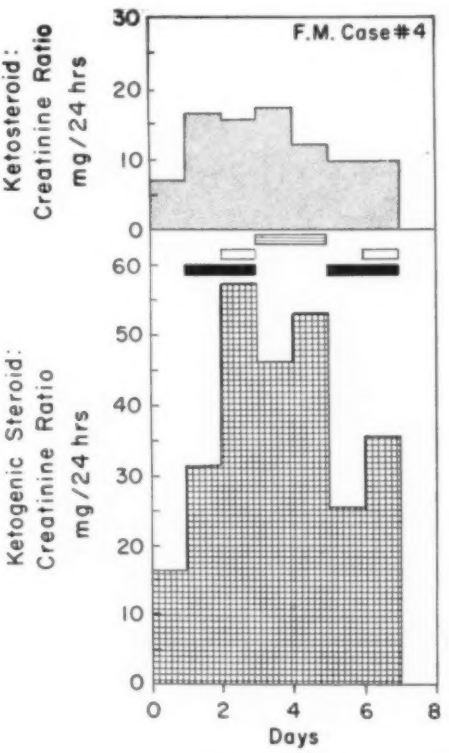


Fig. 4

either pituitary or adrenal insufficiency. The response to prestress SU 4885 in Cases 4, 6, and 8 is diminished when compared with the response to prestress ACTH in the same cases. This is a manifestation of some degree of diminished pituitary ACTH secretion. The urinary 17-KGS, after a poststress challenge with SU 4885, were low in Cases 1 and 8 (as noted in the prestress response). Likewise, the response to poststress SU 4885 in Cases 3, 4 and 6 is diminished, when compared with the response to poststress ACTH, in the same cases. It is apparent then that some degree of diminished pituitary ACTH secretion is present following the stress of $HN_2$ in Cases 3, 4 and 6.

ACTH STIMULATION. The urinary 17-KGS, after a prestress challenge with ACTH, were diminished in Case 1 which is compatible with some degree of adrenal insufficiency. Following $HN_2$, the response to ACTH is diminished in Cases 1 and 8. Thus it is apparent in Case 8 that, following the stress of $HN_2$, either the pituitary or the adrenal is failing to respond adequately. When prestress and poststress responses are compared, taking both the ACTH and SU 4885 values into consideration, it may be seen that Cases 3 and 7 manifest some degree of diminished pituitary secretion and that Case 2 manifests increased pituitary response. Cases 4 and 6 continue to reflect the diminished pituitary ACTH secretion in the poststress response that was seen in the prestress response, however, the already compromised pituitary reactivity has been further depressed.

$HN_2$ STIMULATION. The urinary 17-KGS are depressed below baseline levels in Cases 1, 3, 5 and 7 after $HN_2$ stimulation. The response in Cases 4, 6 and 8 indicates that $HN_2$ causes more release of endogenous ACTH

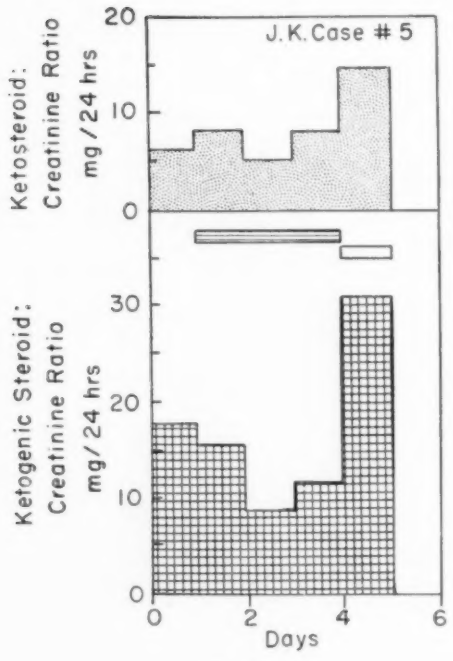


Fig. 5

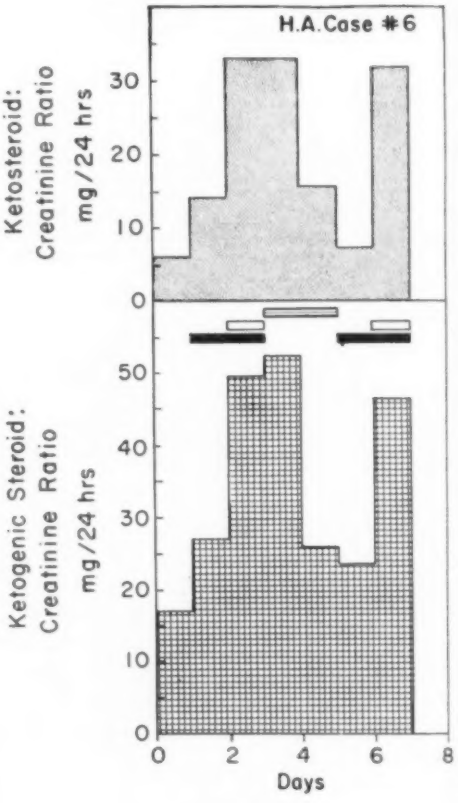


Fig. 6

from the pituitary than does SU 4885. Patients 5 and 9 were not studied prior to $HN_2$ stimulation (Table 1) except for baseline determinations. Case 5 manifests diminished response to $HN_2$, but poststress ACTH stimulation indicates the adrenal has adequate ability to respond. Case 9 reveals stimulation of adrenocortical response above the baseline. The response to $HN_2$, however, was considerably less than that noted after 25 units of ACTH was given. Case 2 reveals a marked response to $HN_2$ stimulation.

**Discussion.** The type and degree of response of the hypothalamic-pituitary-adrenal system is variable following administration of $HN_2$. There may occur stimulation, inhibition or no effect. Withdrawal from exogenous steroids modifies greatly the response to $HN_2$ as noted in 4 of the 9 patients studied.

The development of fever, anorexia, myalgia and arthralgia after withdrawal of steroids has been attributed to a hypoadrenal state. Patient 8 manifested typical symptoms of a hypoadrenal state one week prior to this study. His response to SU 4885 and ACTH, prior to treatment with nitrogen mustard, was indicative of some reduction of ACTH secretion. Nitrogen mustard was capable of stimulating ACTH release sufficient to manifest an adrenal response equal to that produced by exogenous ACTH. However, following the stress of nitrogen mustard, either the pituitary or the adrenal, or both, were incapable of an adequate response; and, even though both organs

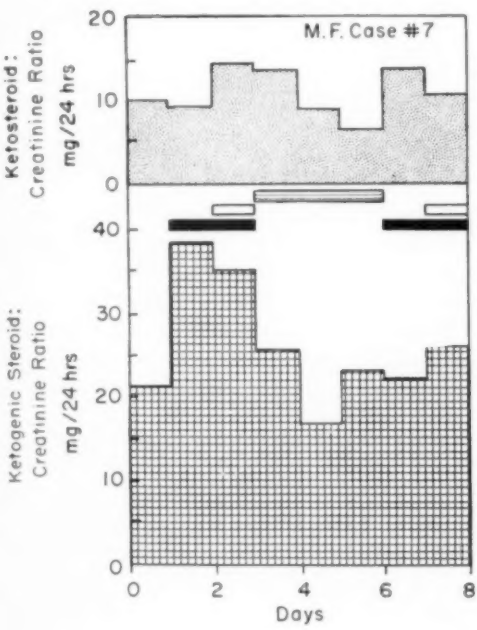


Fig. 7

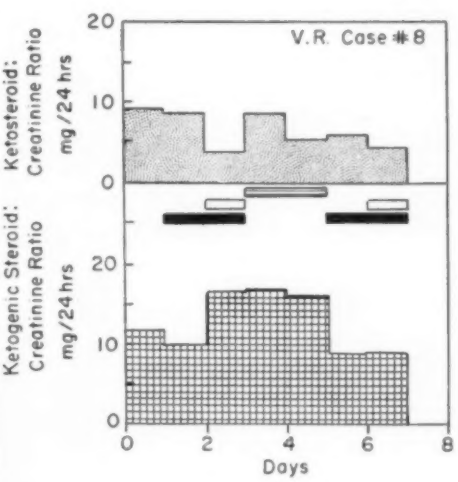


Fig. 8

were capable of responding to $HN_2$, the subsequent responsiveness of neither organ was improved as a result of that stress. Amatruda *et al.*[1] tested the insulin tolerance of patients who had been on prolonged exogenous steroids and found a normal response. Tuberculosis patients treated for prolonged periods of time with ACTH showed a normal response to SU 4885 after withdrawal from exogenous ACTH (Holub, Wallace and Jailer[13]). Holub *et al.* find a diminished response to SU 4885 in patients who have been treated with steroids[11].

Failure of 4 cases (Nos. 1, 2, 5, 7) to respond to the stress of $HN_2$ suggests that the effect of $HN_2$ in these patients was not mediated through the adrenal cortex. The stress did not improve the responsiveness of the adrenal or the pituitary to SU 4885 or exogenous ACTH. Three of these 4 patients had been on exogenous steroids at some time prior to this study (Table 1).

Cases 2, 4, 6 and 8 demonstrate that $HN_2$ is capable, in some instances, of stimulating more release of ACTH than is SU 4885. However, no improvement to the second challenge with SU 4885 or ACTH is noted after the stress of $HN_2$. The results do indicate that the response to SU 4885 is not adequate to evaluate the ability of a patient to react to this type of stress.

The marked stimulation of adrenocortical activity by nitrogen mustard in Case 2 is inconsistent with that noted in the other patients studied. An explanation for this finding is not apparent. The patient also showed an increased response to the second challenge with SU 4885 and ACTH.

Nitrogen mustard has been shown to be an effective stressor agent (Ludewig and Chanutin[21,22], Karnofsky, Graef and Smith[15]). The release of ACTH by the pituitary is increased following stress (Holub, Kitay and Jailer[12]). The mechanism of this release has some relationship to the general adaptation syndrome, and more

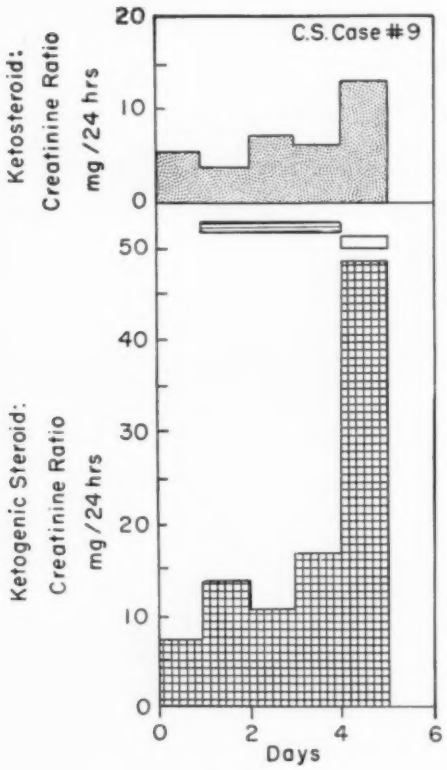


Fig. 9

specifically is related to the effect of increased epinephrine and the level of circulating hydrocortisone.

It is known that epinephrine is capable of stimulating pituitary ACTH release, either directly or through the hypothalamus (Kitay, Holub and Jailer[17,18], Recant *et al.*[25], Sayers[28]). A lesion in the area of the median eminence of the hypothalamus almost completely blocks the stimulatory action of epinephrine (Karnofsky, Graef and Smith[15]). If the supraopticohypophyseal tract is sectioned, pituitary ACTH release in response to acute stress is blocked (McCann and Brobeck[23]). Vasopressin, given intravenously or placed in the third ventricle of dogs, stimulates a marked increase in corticosteroid in adrenal venous blood (Kivaan and Bartelstone[19], McDonald and Weise[24]). Elevation of blood vasopressin is noted after stress and in conjunction with augmented pituitary ACTH discharge (Rothballer[26]).

The level of circulating hydrocortisone is regulated by the rates of production, destruction and utilization of this hormone. The conjugation of steroids for excretion takes place in the liver. The possible effect of $HN_2$ on the ability of liver cells to reduce and conjugate steroids is unknown. However, stress does inhibit conjugation of both reduced and non-reduced ring A corticosteroids (Berliner and Dougherty[3]). Lymphocytes are able to inactivate hydrocortisone by 11-dehydroxylation to form cortisone (Berliner and Dougherty[4]). The antiphlogistic and lymphokaryrrhectic activity of the latter compound is much less than hydrocortisone. Nitrogen mustard destroys lymphocytes with great rapidity and, therefore, may restore the patient's responsiveness to normal levels of exogenous steroid.

Prolonged steroid administration causes adrenal atrophy and pituitary ACTH depletion (Holub, Kitay and Jailer[12,18]). If ACTH is given with the steroids, pituitary ACTH depletion still occurs. Animals exposed to severe stress manifest accelerated discharge of ACTH even if pre-treated with adrenocortical hormone (Sayers[28]). Release of ACTH in response to repeated stress would depend upon the degree of pituitary ACTH depletion prior to stress. It has been shown that rats stressed with scalding water produce less pituitary ACTH release after steroid withdrawal than do normal rats (Holub, Kitay and Jailer[12]) with the stress alone. The fact that the adrenal gland reacts to exogenous ACTH after prolonged corticosteroid therapy does

not mean that it will continue to respond after exogenous ACTH is withdrawn (Carreon, Canary and Kyle[5]).

**Summary.** A quantitative study of the effect of $HN_2$ on the hypothalamic-pituitary-adrenal axis has been described in 9 patients. The type and degree of response was variable. Nitrogen mustard does induce the release of ACTH in some cases, however, it does not improve the ability of the pituitary to respond after this type of stress. The pituitary or adrenal response, or both, is depressed during $HN_2$ therapy in some patients. The pituitary response to SU 4885 does not necessarily assess the ability of the pituitary to respond to the stress of $HN_2$. The mechanism of pituitary release of ACTH as a result of the stress of $HN_2$ is discussed.

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# WATER INTOXICATION AFTER HYPOPHYSECTOMY: AN UNUSUAL CASE*

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In recent years, great interest has been focused on unusual syndromes characterized by hyponatremia and water retention in a variety of disease states including neoplastic disease and cerebral disorders. In recent articles, Schwartz *et al.*[10,11] have described 3 patients with bronchiogenic carcinoma who developed hyponatremia in association with water intoxication. After careful study of water balance, these authors demonstrated that an inappropriate secretion of antidiuretic hormone was the probable defect.

Hyponatremia has been noted following surgical hypophysectomy, as utilized in the palliation of metastatic mammary carcinoma (Lipsett *et al.*[5], Maclean *et al.*[6]). Glucocorticoid insufficiency is a prominent factor in many of these cases. In the absence of adrenocortical insufficiency, this phenomenon has been shown to be related to water retention, usually subsequent to vasopressin administration (Lipsett *et al.*[5]). Leaf *et al.*[4] demonstrated some years ago that urinary salt loss is a reversible concomitant feature of the water intoxication syndrome. Similar syndromes have been noted in patients with cerebral disease and again the etiology may be that of water intoxication with renal sodium wasting being only a secondary manifestation (Goldberg and Händler[3], Schwartz, Tassel and Bartter[11]).

As far as the authors know, the syndrome of hyponatremia associated with water intoxication and renal salt wasting has never been reported in an hypophysectomized patient who has been treated adequately with adrenocorticoids and who has not received vasopressin. It is such a case we wish to report here.

**Case Report.** M.R., a 58-year-old Caucasian woman underwent a left radical mastectomy for infiltrating intraductal carcinoma on July 21, 1959. Metastatic lymph nodes were found in the left axilla at time of surgery. In November, 1959, severe persistent back pain developed and a spontaneous fracture of the 12th thoracic vertebra was discovered by roentgenogram. Conventional and cobalt irradiation was applied, but pain persisted and later Roentgen-ray examination revealed another spontaneous fracture of the 9th thoracic vertebra. Despite the use of a back brace and general supportive measures, the patient's course was downhill with severe pain, anemia, vomiting, and weight loss. She was admitted to UCLA Medical Center in March, 1960. The patient's past history was significant only in that she had suffered a cerebral vascular accident 2½ years prior to admission with a transient right hemiplegia. The patient had undergone a total abdominal hysterectomy in 1944 for leiomyomata of the uterus.

Physical examination on admission revealed

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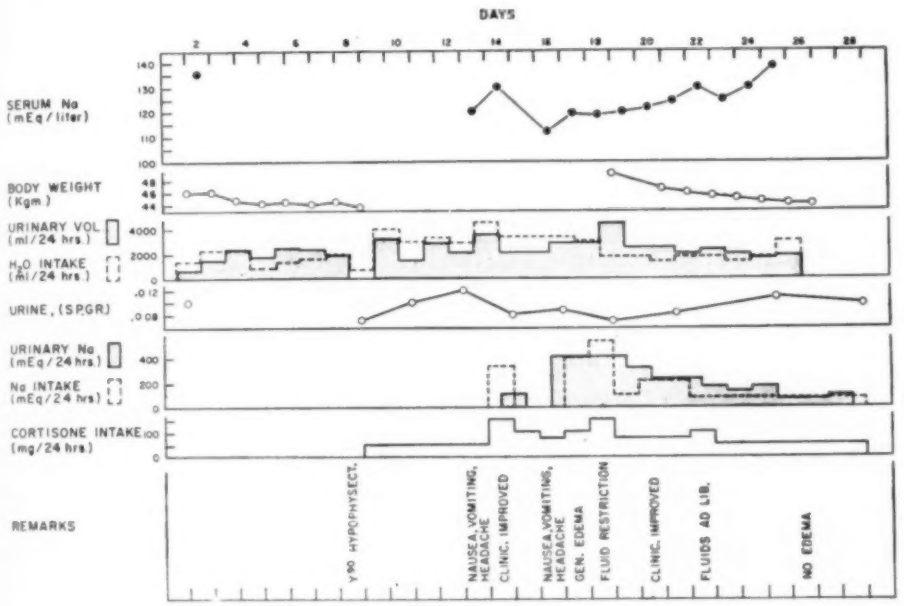


Fig. 1.—Metabolic studies on M.R.

a well developed, thin, pale, chronically ill woman. Positive findings included an incompletely healed left radical mastectomy incision, a grade II harsh systolic murmur heard best at the 4th intercostal space, and marked tenderness to palpation over the dorsal vertebrae with moderate limitation of upper trunk movement due to pain.

Laboratory examinations were as follows: hemoglobin 10.4 gm., packed cell volume 33.5% and leukocytes of 7,700 with normal differential. Urinalysis was normal as were serum electrolytes (serum sodium 136 mEq. per L.). Serum calcium was 4.4 mEq. per L., phosphorus 1.9 mEq. per L., alkaline phosphatase 11.5 K-A units, and 24-hour urinary calcium excretion was 52.4 mg. Serum creatinine was 1.3 mg. per 100 ml. and multiple determinations throughout the patient's hospital course revealed little variation from this figure, with a maximum value of 1.5 mg. per 100 ml. The BUN was 32 mg. per 100 ml., the BSP retention was 6.6% at 45 minutes, and the total protein was 7.7 gm.% with 3.2 gm.% albumin and 4.5 gm.% globulin. A Hickey-Hare test was normal as was a water load test, in which the patient was able to excrete 700 ml. of a 1000 ml. water load in 4 hours with a drop of urine specific gravity to 1.002. The PBI was 4.0 $\mu$g. and the $I_{131}$ uptake was 28.5% in 24 hours. Roentgenograms revealed a normal chest and the fractures of $T_9$ and $T_{12}$, as well as a lytic defect in the right inferior pubic ramus.

On the eighth day of hospitalization under general anesthesia 4 $yttrium_{90}$ oxide beads totaling 9.6 mc. were implanted on each side of the pituitary gland by the stereotaxic procedure of Rand[8]. Roentgenographic studies revealed satisfactory placement of the beads within the sella turcica. The patient tolerated the procedure well and was transfused, because of anemia, with 2 units of whole blood. She was given 50 mg. of cortisone acetate daily (Fig. 1). The first 3 postoperative days were uneventful with the patient feeling well except for a generalized headache. On the fifth postoperative day the patient complained of increased headache, weakness, tremulousness, nausea and vomiting. Vital signs were normal. Serum electrolytes revealed a moderate hyponatremia (120 mEq. per L.) and hypochloremia (86 mEq. per L.), with normal potassium and $CO_2$-combining power. The patient was given intravenous isotonic sodium chloride and placed on parenteral hydrocortisone hemisuccinate (Fig. 1.—expressed as cortisone equivalent). The urinary output was adequate at all times. Within 24 hours (day 14) the patient was asympto-

matic and her serum sodium was higher although still not normal (130 mEq. per L.).

The patient then felt well and was to be discharged but on day 16 symptoms of nausea, tremulousness and weakness recurred. Severe hyponatremia was now present (serum sodium 109 mEq. per L.). The patient was again given increased amounts of hydrocortisone and hypertonic saline intravenously. On day 17 the serum sodium had risen to 118 mEq. per L. and generalized edema was noted. The patient was found to have gained 5 kg. since the day of surgery. Determination of blood volume using radioiodinated serum albumin on this date was 6310 ml., compared to a predicted normal of 3500. Urinary aldosterone* was less than 1 μg. per 24 hours. At this point, a diagnosis of water intoxication was seriously considered and fluids were moderately restricted and the intake of sodium chloride increased to 12 gm. per day. On this regimen, the patient gradually gained strength, a slow but consistent rise in serum sodium occurred and a diuresis was initiated. On day 23 the patient was given a 4-gm. sodium intake with fluids *ad lib.* She continued to improve with gradual rise in serum sodium and chloride to normal levels, loss of edema and decrease in all of her symptoms. A second radioisotopic determination of blood volume on day 24 was 3000 ml.; the excretion of urinary aldosterone on that date was 1 μg. per 24 hours. During this period the patient received 50 mg. of cortisone orally per day.

A water-load test performed on day 26 revealed excretion of 950 ml. of an administered 1000 ml. load in 4 hours. Urinary specific gravities while on fluids *ad lib.* and a 4-gm. sodium diet ranged between 1.005 and 1.016. After the initial diuresis, polyuria did not occur.

Subsequently evidence of degree of hypophyseal destruction was as follows: urinary gonadotropin fell from the preoperative level of greater than 40 mouse units to consistent postoperative levels of less than 5 mouse units; $I_{131}$ uptake fell to consistently less than half the preoperative levels (6 weeks after operation, 8.4% in 24 hours); serum PBI fell to 3.5 μg. Diabetes insipidus has not occurred. Twenty-four-hour urinary aldosterone on an *ad lib.* diet was 2 μg., a low normal figure.

The patient has done exceedingly well since discharge from the hospital. She has had consistent slow weight gain with absence of back pain and has resumed many household activities. Her serum electrolytes have remained consistently within normal limits and she is considered to have had at least an excellent subjective remission of her disease. She receives a regular diet and has no restrictions or supplementations of fluids or salt. At no time has there been evidence of damage to the central nervous system.

**Discussion.** This patient presented an interesting and difficult management problem. The development of severe and symptomatic hyponatremia led initially to the diagnosis of a salt losing syndrome probably due to adrenocortical insufficiency, perhaps complicated by inadequate salt intake. The treatment that was initiated (increased adrenocortical steroids and sodium chloride infusions) was rapidly effective. The improvement was transient, however, and the symptoms and hyponatremia returned in a more severe form in a few days. It was then, after the appearance of edema and the discovery that the patient had gained a considerable amount of weight, that water intoxication was considered. The antithesis, diabetes insipidus, has occurred in 4 of 17 patients subjected by us to yttrium$_{90}$ hypophysectomy (Rand *et al.*[9]). Only when diabetes insipidus occurs and the patient is treated with vasopressin, have water intoxication and hyponatremia resulted after yttrium$_{90}$ or surgical hypophysectomy in our series.

Evidence that this patient developed water intoxication consisted of increase in weight and the development of edema and hypervolemia. Thus a primary renal salt loss is not an adequate explanation for the occurrence of hyponatremia. At the same time, although not the primary event, inability to conserve sodium was indeed present, as evidenced by continued high levels

*(Normal value 2 to 23 μg. per 24 hours) Performed at Bio Science Labs by method of Sobel *et al.*, J. Clin. Endocrinol., **19**, 1302, 1959.

of sodium excretion despite a low serum sodium concentration.

Primary renal disease is not likely in this case considering the normal urine sediments and creatinine determinations throughout her hospital course. The patient was able to excrete a water load preoperatively as well as at the conclusion of the balance period, which further implies that the abnormal process was an acute and transient one.

Adrenal insufficiency is most unlikely as a cause of the abnormality in this case. At no time during the postoperative period had she received less than 50 mg. of cortisone or its equivalent. For much of the time during hospitalization, her adrenal steroid replacement therapy was at much higher dosage levels (Fig. 1). Also despite improvement, diuresis was not produced by the increased steroid dosage. It is possible, however, that her early improvement after the first episode of hyponatremia was in part due to sodium retention engendered by the increased dosage of adrenal steroids. Another fact which supports the conclusion that the patient was not in adrenal insufficiency was the normal water-load test performed at the conclusion of the balance period while the patient was receiving 50 mg. of cortisone.

Vasopressin was not administered to this patient at any time postoperatively. It was discovered, however, that the patient was being encouraged to drink by the nursing staff, even when she was not thirsty, and that she was, according to her intake and output chart, in positive water balance throughout the early postoperative period. Unfortunately, the patient was not weighed during this time. Following restriction of water and the addition of a sodium supplement to her diet, a diuresis occurred and the serum sodium began to rise. The fact that this improvement continued even when the supplementary salt was reduced from 12 gm. to 4 gm. per day implies that water restriction was the major therapeutic factor.

The salt losing process was demonstrated by the extremely high sodium excretion, particularly following the initial hyponatremia episode when the serum sodium was below 120 mEq. per L. Despite the large sodium intake, insufficient sodium was retained to counter the severe hypotonicity of the patient's serum except when large doses of adrenal steroids were administered. A similar phenomenon of salt wasting secondary to water intoxication and improved by steroid administration has been well documented by Schwartz *et al.*[11]. The mechanism of salt losing is unknown but three contributory factors might well be involved. Firstly, it is well established that hypervolemia leads to a reduction in the secretion of aldosterone by the adrenal cortex (Bartter *et al.*[1]). Secondly, hypervolemia results in an increase in glomerular filtration rate with a secondary increase in the filtered load of sodium. More speculative is the possibility that the renal mechanism for absorption of sodium may be impaired when water intoxication is present.

Our patient showed subsequent evidence that function of the adenohypophysis had been markedly impaired. In this connection, Dingman *et al.*[2] recently reported several patients demonstrating hypoaldosteronism in panhypopituitarism. One of their patients had breast cancer and had been treated by hypophysectomy. This patient developed postoperative hyponatremia requiring both cortisone and mineralocorticoid therapy, withdrawal of which precipitated mild adrenal crisis and depressed aldosterone excretion values. Two other patients with untreated postpartum pituitary necrosis also de-

veloped hyponatremia and decreased urinary aldosterone levels during adrenal crisis. These investigators concluded that there was preservation of sodium homeostasis in hypoaldosteronism by protective or potentiating action of cortisone. These conclusions may be questioned in the light of our experience. In our patient, hypoaldosteronism, as implied by decreased urinary excretion of aldosterone, was present despite adequate or superabundant adrenal replacement therapy. It is probable that aldosterone secretion in our patient was depressed because of the water intoxication and hypervolemia. Subsequent urinary aldosterone excretion was low normal on ordinary diet. Such a process may occur in adrenal insufficiency where water excretion is impaired. Although hypophysectomy has been shown to affect aldosterone secretion to a certain, probably slight degree, practically speaking it is of little importance in the management of hypophysectomized patients (Lipsett *et al.*[5], Maclean *et al.*[6], Pearson[7]). It is rarely necessary to treat hypophysectomized individuals with mineralocorticoids.

The presence of serum hypotonicity accompanying relative urinary hypertonicity has been construed as strong evidence for inappropriate ADH secretion (Schwartz, Tassel and Bartter[11]). Such was the situation in our patient and an inappropriately excessive secretion of antidiuretic hormone (ADH) appears most likely as the primary explanation for her disorder. The cause of this inappropriate ADH secretion, particularly in an individual who has undergone hypophysectomy requires elucidation. It is conceivable that irritation of the neurohypophysis led to a transient, uncontrolled elaboration of ADH. This has not been described previously as a complication of implantation hypophysectomy and it has not been noted in our other patients (Rand *et al.*[9]). On the contrary, as was previously mentioned, diabetes insipidus occurred in about one-fourth of our patients subjected to yttrium$_{90}$ implantation and several others have developed minor reduction in posterior pituitary function; that is, abnormal Hickey-Hare tests without symptomatic diabetes insipidus. In this patient diabetes insipidus has not yet appeared. In the light of the fact that more and more patients are undergoing hypophysectomy for various neoplastic and other diseases, the possibility of excessive ADH elaboration must also be kept in mind.

**Summary and Conclusions.** 1. The occurrence of transient, symptomatic hyponatremia after yttrium$_{90}$ hypophysectomy is described in a patient who received adequate glucocorticoid medication and no vasopressin.

2. The data support the conclusion that water intoxication was the primary event and that hyponatremia, hypoaldosteronism, and urinary salt wasting were secondary manifestations.

3. It is suggested that the disorder was caused by the inappropriate secretion of antidiuretic hormone, possibly related in turn to neurohypophyseal irritation due to irradiation by implanted yttrium$_{90}$.

ADDENDUM: Since the time of writing, we have observed and studied 7 entirely similar cases of water intoxication occurrng after hypophysectomy. Interestingly, 2 cases appeared following transcranial surgical removal of the pituitary. All cases promptly responded to simple water restriction as the sole therapeutic measure. This, we feel, adds weight to our conclusions regarding the occurrence of the syndrome in relation to hypophyseal surgery and supports the probability that uncontrolled ADH elaboration may occur in response to trauma of the hypophyseal-hypothalamic area.

ACKNOWLEDGMENT: Grateful acknowledgment is made to Drs. D. H. Solomon and C. R. Kleeman for their suggestions in the preparation of this manuscript.

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## SUMMARIO IN INTERLINGUA

### Intoxication per Aqua post Hypophysectomia: Un Caso Inusual

1. Es describite le occurrentia de un transiente hyponatriemia symptomatic post hypophysectomia a yttrium$_{90}$ in un patiente recipiente un adequate medication glucocorticoide e nulle vasopressina.

2. Le datos supporta le conclusion que intoxication per aqua esseva le evenimento primari e que hyponatriemia, hypoaldosteronismo, e perdita urinari de sal esseva manifestationes secundari.

3. Es opinate que le disordine esseva causate per le secretion inappropriate de hormon antidiuretic, possibilemente relationate—de su parte—con un irritation neurohypophysee per radiation ab le implantate yttrium$_{90}$.

## SUMMARIO IN INTERLINGUA

*(See page 766 for original article)*

### Correction de Responsas Erratic a Hypnoticos in Subjectos de Etates Avantiate

In patientes de etates plus tosto avantiate, le administration de hypnoticos pote evocar un excitation erratic. Le addition de phenyltoloxamina a secorbarbital permitte le uso de un plus basse dosage del hypnotico, restringe le phase excitatori, effectua un prompte e plus satisfacente somnio, e reduce le incidentia de somnolentia procrastinante. Le combination de iste drogas in un sol tabletta resulta in un salve e efficace hypnotico pro personas de etate avantiate. Illo ha nulle significative effectos lateral.

# THE ELECTROCARDIOGRAPHIC CHANGES IN ACUTE PHOSPHORUS POISONING IN MAN*

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There is enough clinical evidence to suggest that death from acute phosphorus poisoning is mainly governed by the amount of the element absorbed from the gastrointestinal tract, ensuing early, when there results an overwhelming toxemia with anoxia of the cells of vital organs; and delayed, when the absorption is slow, or the amount ingested is small. Death always follows a definite pattern with evidence of failure of the circulation. Once large amounts of the poison are absorbed, the inexorable outcome is death.

It appears as if death within the first 12 hours invariably results from peripheral vascular collapse due either to the direct or indirect effect of the poison on the cardiovascular system. Death within 24 to 48 hours may ensue from peripheral vascular collapse, but the clinical picture is frequently accompanied by signs of acute renal failure. Death within 48 to 72 hours may result from peripheral vascular collapse or cardiac arrest, but renal and hepatic damage are invariably present. Survival for 3 days or more is by itself a good prognostic sign, but death may result from a combination of hepatic, renal and cardiac failure. Death from hypoglycemia is infrequent and generally delayed after 2 days following the intoxication.

These observations based on an analysis of a large series of cases of acute phosphorus poisoning for suicidal intent (Díaz-Rivera *et al.*[2]) has led us to explore the effect of the poison on the cardiovascular system with special emphasis on the electrocardiographic alterations. This study is justified by the paucity of publications on this subject (Dathe and Nathan[1], Newburger, Beaser and Shwachman[4]).

**Material and Methods.** From 1948 to 1958, 59 suicidal intents with yellow phosphorus were studied in 55 patients. The diagnosis was based on previously established criteria

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(Díaz-Rivera *et al.*[2]). A careful clinical evaluation was made to eliminate concurrent or secondary cardiac disorders which may have altered the electrocardiographic patterns.

The patients were otherwise physically healthy with ages ranging from 16 to 45 years, of whom 35 were males and 18 females. All ingested the element in the form of a rat exterminator known as "rat paste" or "electric paste," sold in collapsible tubes in drug, grocery and hardware stores, with a net weight of 62.5 gm. and containing 2.5% (1.57 gm.) of the element as such. The approximate amount of the poison ingested was determined by measuring the remainder in the containers brought in by relatives, or from reliable information obtained from the patients or close members of their families. On the basis of this criterion, it was discovered that the approximate amount taken varied from 0.22 to 1.5 gm., and that 15 had ingested 1.5 gm.; 23 from 0.75 to 1.4 gm.; 11 from 0.39 to 0.74 gm., and 6 less than 0.38 gm. The amount of the poison ingested was unknown in 2 instances.

Water was employed as a vehicle in 18 instances, alcoholic beverages in 15, and food in 10. The remaining 14 took the poison straight from the tube or used solid foods as vehicles (cheese, cake, bread, and the like). Prior to the electrocardiographic studies, gastric lavage with large amounts of a 1:1,000 solution of potassium permanganate was given to 52 patients; 34 within the first hour, 11 within 4 hours, and in 7, more than 6 hours after the poisoning. Seventeen suffered from nausea and vomiting and 4 had diarrhea prior to the electrocardiographic studies.

The temperature, pulse rate and blood pressure were carefully observed. Red and white cell counts and hemoglobin values, urinalyses, fasting blood sugar, nonprotein nitrogen, and icterus indices were repeatedly done. Serial electrocardiograms were done in 39 instances: within the first 24 hours in 21; during the second day in 5; on the third day in one; during the fourth to eighth days in 9, and after the eighth day in 3.

Besides the gastric lavage the patients received daily intravenous infusions of 2,000 to 4,000 ml. of 5% glucose in normal saline solution, and a high caloric diet was started as soon as tolerated. Parenteral multivitamins were routinely given.

**Results.** The electrocardiograms were abnormal in 33, borderline in 3 and normal in 23 cases. Seventeen cases revealed abnormal T-waves consisting of either inversion in lead 1 or leads V4-V6, or both, or marked, discordant flattening in these leads with subsequent recovery. Seven of the tracings showed more than one alteration con-

TABLE 1.—SUMMARY OF ALTERATIONS IN THE ELECTROCARDIOGRAM IN 33 CASES OF ACUTE PHOSPHORUS POISONING

| | |
|---|---|
| Abnormal P waves | 2 |
| Prolonged P-R interval | 1 |
| Right Bundle Branch Block | 1 |
| Delayed Intraventricular Conduction | 1 |
| Prolonged Q-T interval | 6 |
| Ventricular Fibrillation | 2 |
| Nodal Rhythm | 2 |
| Low Voltage of QRS | 2 |
| Abnormal S-T segments | 4 |
| T wave changes | 17 |

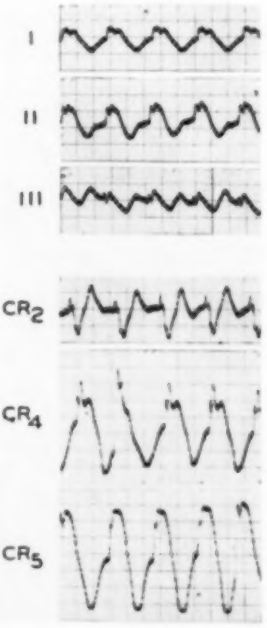


Fig. 1.—Electrocardiographic alterations on a 19-year-old male admitted 1 hour after the ingestion of 1.5 gm. of yellow phosphorus diluted in rum. He died 3 hours after admission. The electrocardiogram is indicative of ventricular tachycardia. The heart was normal on postmortem examination.

sisting of prolongation of the Q-T interval as well as T wave changes in 3; S-T segment and T wave alterations in 2; a nodal rhythm with T wave changes in 1, and prolongation of Q-T interval and significantly low voltage of the QRS complexes in one. A shifting pacemaker, unifocal premature ventricular beats and doubtful T wave changes were observed in the borderline tracings. Bradycardia was evident in 3 of the normal and 5 of the abnormal electrocardiograms (Table 1) (Figs. 1 to 3).

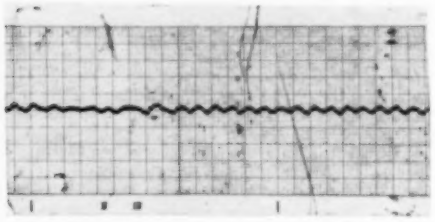

Fig. 2.—Electrocardiographic alterations on a 20-year-old colored male admitted to the hospital 15 minutes after the ingestion of 1.5 gm. of yellow phosphorus. His stomach was lavaged with undeterminded amounts of 1:1000 potassium permanganate solution. His blood pressure on admission was 96/60, soon not obtainable, with death from peripheral vascular collapse 4 hours after admission. Necropsy revealed a normal heart, a fatty liver and atrophy of the cerebral cortex. The tracing is indicative of ventricular fibrillation.

No correlation could be established between the electrocardiographic findings and the age, sex, blood pressure levels, the hemoglobin values, vomiting, diarrhea and the vehicle utilized for the ingestion of the poison. However, there seems to be some correlation of the recorded abnormalities with the amount of poison ingested. Thus, definite electrocardiographic abnormalities were noted in 11 of the 15 patients who ingested 1.5 gm. of the element; in 13 of the 23 who ingested 0.75 to 1.4 gm.; in 5 of the 11 who ingested 0.39 to 0.74 gm., and in 2 of the 6 who took less than 0.38 gm. (Table 2). These observations tend to suggest that the electrocardiographic alterations are mainly governed by the quantity ingested and the proportional amount absorbed from the gastrointestinal tract, and that the early development of these abnormalities may serve to measure the severity of the intoxication.

TABLE 2.—CORRELATION OF ELECTROCARDIOGRAPHIC ALTERATION WITH THE AMOUNT OF YELLOW PHOSPHORUS INGESTED

| *Amount of Phosphorus in gm.* | *Cases* | *Abnormal* | *Borderline* |
|---|---|---|---|
| Less than 0.38 | 6 | 2 (33%) | — |
| 0.39 to 0.74 | 11 | 5 (45%) | — |
| 0.75 to 1.49 | 23 | 13 (56%) | 2 |
| 1.5 or over | 15 | 10 (67%) | 1 |

A definite correlation was established between the electrocardiographic abnormalities and the icteric indices (Table 3). Thus, it seems plausible to assume that the degree of hepatic, renal, and myocardial involvement is a reflection of the amount of phosphorus absorbed (Table 4).

TABLE 3.—CORRELATION OF THE ICTERIC INDEX WITH THE ELECTROCARDIOGRAPHIC ALTERATIONS

| *Icteric Index (Units)* | *Cases* | *Abnormal* | *Borderline* |
|---|---|---|---|
| 0–7 | 17 | 9 (53%) | 2 |
| 8–15 | 15 | 6 (40%) | 0 |
| 16–14 | 13 | 10 (80%) | 0 |

TABLE 4.—CORRELATION OF AZOTEMIA WITH THE ELECTROCARDIOGRAPHIC ALTERATIONS

| *Highest NPN (mg./100 ml.)* | *Cases* | *Abnormal* | *Borderline* |
|---|---|---|---|
| 40 or less | 30 | 13 (43%) | 2 |
| 41 to 69 | 14 | 12 (86%) | 0 |

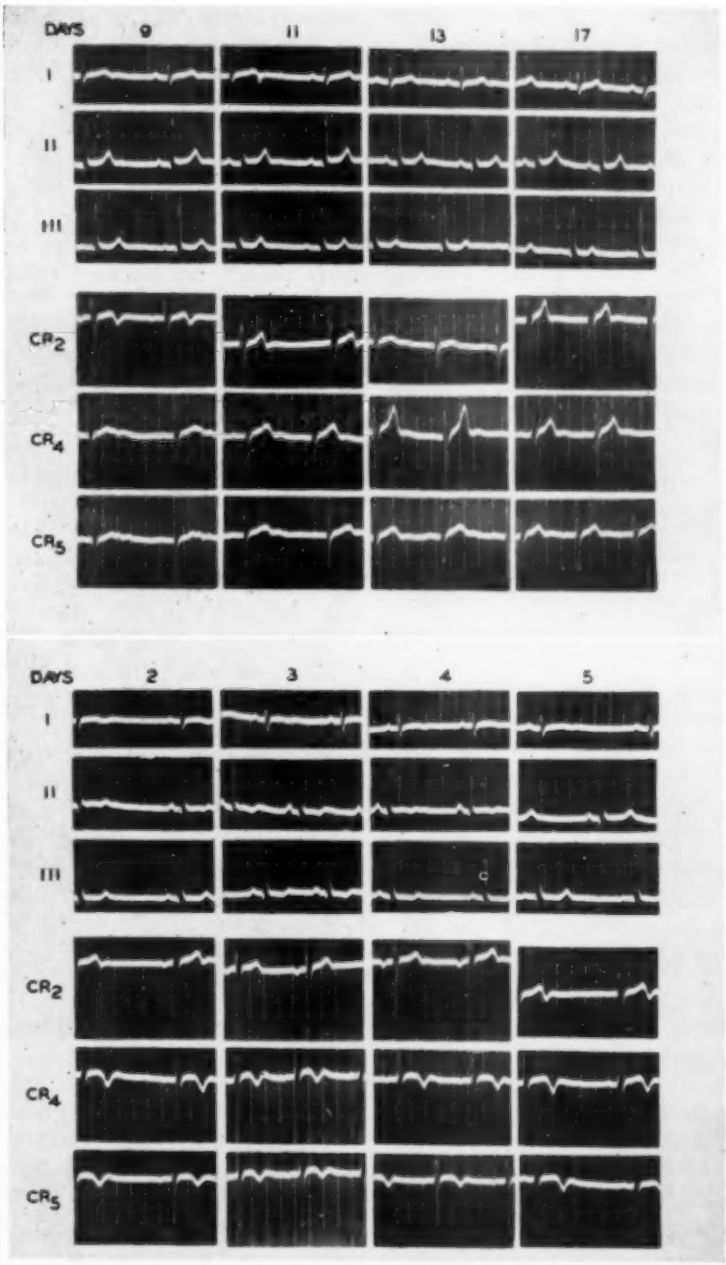


Fig. 3.—Electrocardiograms of a 31-year-old chronic alcoholic who ingested an unknown amount of rat paste during one of his frequent sprees. There is evidence of transitory myocardial damage attributable to the effects of the poison on the myocardium. Note the serial electrocardiographic alterations mainly dominated by T waves changes with improvement after the 13th day.

In 18 of the serial electrocardiographic studies, 8 were abnormal from the outset while in 10, the alterations were delayed. Twenty-two of the 41 tracings taken during the first day of illness were abnormal, 2 were borderline and 17 appeared normal. Four of the 5 examined on the second day, and 7 of the 13 on the third day were abnormal (Table 5). These observations tend to indicate that the toxic effect of yellow phosphorus on the myocardium may be delayed either by slow or diminished absorption from the gastrointestinal tract.

TABLE 5.—THE RELATIONSHIP OF THE DURATION OF POISONING AND THE INITIAL ELECTROCARDIOGRAPHIC STUDY

| *Time (Days)* | *Cases* | *Abnormal* | *Borderline* |
|---|---|---|---|
| 1 | 41 | 22 | 2 |
| 2 | 5 | 4 | — |
| 3 | 1 | 1 | — |
| 4–7 | 9 | 4 | — |
| 8–10 | 3 | 2 | 1 |

Electrocardiographic abnormalities consisting of ST and T wave changes were recorded in 4 of the 6 patients with abnormally high serum calcium values but no shortening of the QT interval was present. Twelve patients showed a high serum phosphorus with 4 definitely abnormal electrocardiograms and one borderline tracing. The possible relation of these electrolyte disturbances with the electrocardiographic findings of these limited samples remains unassessed. By the same token, the phenomenon of hypercalcemia in the presence of normal or high serum phosphorus remains unexplained.

The mortality rate was 16%. Of the 9 deaths, 6 occurred within the first 27 hours and the other 3, on the third, fifth and thirteenth days after the ingestion of the poison respectively. Death was attributed to peripheral vascular collapse in 7, to hepatic coma in one and to hypoglycemia in the other. It was interesting to observe that there were 6 abnormal and one borderline tracings among these patients (Table 6).

Necropsy was performed in 3 cases. A definitely abnormal electrocardiogram with marked ST depressions was encountered in a patient (Case 12) 48 hours after the ingestion of the poison and in whom the postmortem examination revealed fatty degeneration of the myocardium. The electrocardiogram as well as the postmortem findings were normal in the other patient (Case 5). Ventricular tachycardia

TABLE 6.—VARIOUS CLINICAL PARAMETERS IN FATAL CASES OF PHOSPHORUS POISONING

| *Case No.* | *Dose (mg. of P)* | *Time Lavage (hrs. after ingestion)* | *Death (hrs.)* | *Icteric Index* | *NPN* | *Time EKG after ingestion (hrs.)* | *Result E K G* |
|---|---|---|---|---|---|---|---|
| 5 | 375 | 0.5 | 13 | 6.3 | 37 | 1.5 | Normal |
| 6 | 750 | 1 | 10 | — | — | 1.5 | Normal |
| 11 | 750 | 2 | 10 | — | — | 2 | Borderline |
| 12 | 250 | 7 | 67 | — | — | 48 | Abnormal |
| 20 | 750 | 1 | 13 days | 93 | 44 | 24, 48, 216, 264 | Abnormal |
| 36 | 750 | 0.5 | 27 | — | 35 | 18 | Abnormal |
| 52 | 1,500 | 1 | 5 days | 36 | — | 24, 72, 120 | Abnormal |
| 54 | 1,500 | 1 | 4 | — | — | 4 | Abnormal |
| 55* | 1,500 | 1 | 5 days | 9.2 | — | 24, 48, 120 | Abnormal |

*Hypoglycemia, severe

preceded death in Case 54 (Fig. 1) and in whom the myocardium was normal on postmortem examination.

COMMENT. When certain poisons taken by man either by accident, or for therapeutic, suicidal and other purposes are improperly detoxified or incompletely eliminated, toxic manifestations pointing to disturbances of cardiovascular function may supervene with, or without detectable pathological alterations in the heart and blood vessels. Frequently, mention is made of the toxic effects of digitalis, quinidine, potassium, the antimonials (fuadin, anthiomaline and tartar emetic) (Díaz-Rivera *et al.*[3]), but rarely of yellow phosphorus.

Yellow phosphorus is a powerful protoplasmic poison (minimum lethal dose, 10 mg.) which can produce serious hepatic, cerebral, renal and cardiovascular impairment, with death from circulatory failure in the majority of instances, and which is capable of producing electrocardiographic alterations.

An analysis of the data pertaining to the alterations in the cardiovascular system gathered from the study of 53 cases of acute phosphorus poisoning for suicidal intent would tend to indicate that intoxication with yellow phosphorus carried a high mortality (16% in this series), and that the most important prognostic factor is the amount of the poison ingested and the rapidity of its absorption. This is evidenced by the higher mortality among those who ingested the poison in a liquid vehicle, especially with alcoholic beverages favoring its rapid absorption. It seems as if early gastric lavage and early vomiting may have been protective among those patients who ingested doses of 0.78 gm. or less. For larger doses the prognosis is grave even when the stomach is emptied spontaneously. Among the latter, shock, as demonstrated by low blood pressure levels, points to an early death. This phenomenon was also observed among those fatal cases from smaller amounts of the poison in whom death is generally preceded by failure of the circulation.

It must be emphasized that the great majority of the cases of acute phosphorus poisoning die before the advent of a clear-cut clinical picture of hepatic damage, but the rapid onset of clinical jaundice is a very serious prognostic sign in the majority of instances. However, since this phenomenon depends upon the amount of the element ingested, the appearance of jaundice after the third day is generally of little prognostic value.

It must be re-emphasized that the most valuable signs of impending death are the early onset of shock and coma, especially when these are preceded by severe restlessness, delirium and toxic insanity resulting from an overwhelming toxicity of the cells of the central nervous system (toxic encephalitis) (Díaz-Rivera *et al.*[2]). Death may be produced by uremia if azotemia appears early after the intoxication. If the retention of nitrogenous waste products is delayed after the third day, recovery is the rule. Whether the renal damage results from the direct effect of the poison or from the severe hemodynamic alterations so frequently observed among these patients remains a moot question. However, the latter is the favored mechanism to explain the rapid onset of uremia terminating in death. Hypoglycemia may lead to death within 12 to 24 hours, but it is generally observed 2 days after the ingestion of the poison. This phenomenon may be indicative of extensive liver damage.

It was evident that death within the first 12 hours results from acute peripheral vascular collapse due to either a direct or indirect effect of the poison

on the cardiovascular system. Death within 24 to 48 hours may be due to peripheral vascular collapse, but the clinical picture may be accompanied by signs of acute renal failure. Death within 48 to 72 hours may result from peripheral vascular collapse or ventricular fibrillation, but signs of renal damage are present. Survival for 3 days or more is a sign of good prognosis, but death may still result from a combination of hepatic, renal and cardiac failure.

The intensification of symptoms after 48 hours observed among those who ingested smaller amounts of the poison remains unexplained. It seems clear to us that the mechanism of death in acute phosphorus poisoning is mainly governed by the amount absorbed, death supervening early when there results an overwhelming toxemia with anoxia of the cells of vital organs; and delayed, when the absorption is slow or the amount ingested small, but always following a definite pattern, with death from failure of the circulation (Díaz-Rivera *et al.*[2]).

As demonstrated by the data collected from studies on the electrocardiographic changes, it is evident that yellow phosphorus may produce extensive damage to the myocardium. When reversible, these alterations may persist for 3 weeks or longer. Since this element is a powerful protoplasmic poison it may be assumed that the electrocardiographic changes may result from a direct action on the myocardium. The early deaths from ventricular fibrillation may well substantiate this assumption. However, it seems to us that in some instances the effect of the poison in the peripheral circulation (peripheral vascular collapse) may deprive the heart of an adequate venous return, with a decreased cardiac output and hence, a decreased coronary blood flow resulting in an extremely severe myocardial ischemia leading to death.

Whether toxic products arising from the extensively damaged liver, kidney, brain, and other organs play a role in the production of the electrocardiographic alterations remains to be determined. However, it must be emphasized that the liver is heavily infiltrated with fat as early as 6 hours after a serious intoxication rendering its detoxifying functions inadequate (Díaz-Rivera *et al.*[2]). By the same token it is assumed that the renal function is markedly altered from early in the course of illness. It must be emphasized that the higher incidence of electrocardiographic alterations were observed among those with the highest nonprotein nitrogen retention and icterus indices. The possibility of a severe degree of toxic myocarditis, accompanied by extensive toxic hepatitis, nephritis and encephalitis may be a simpler explanation. This is best illustrated by the rapid appearance of electrocardiographic changes within the first 24 hours following the ingestion of the larger amounts, and their appearance delayed with smaller doses of the element.

No corroborative laboratory data is presented to suggest the role of hypoglycemia, or the alterations in the serum potassium, calcium, phosphorus or magnesium in the production of the electrocardiographic alterations in this sample. It seems that in view of the recognized cardiac anatomopathological alterations directly caused by yellow phosphorus, these may represent the main governing factors in the production of the abnormalities in the electrocardiogram. These myocardial changes whenever marked may be incompatible with an adequate cardiac function leading to death from a low cardiac output or serious alterations in cardiac rhythm.

**Summary.** An analysis of the electrocardiographic findings in 55 patients who had 59 suicidal attempts with yellow phosphorus revealed significant abnormalities in 33 consisting of prolongation of QT interval, ST and T wave changes, abnormalities in rhythm and low voltage of QRS complexes. Borderline tracings were encountered in 3 additional cases. The incidence of electrocardiographic abnormalities was directly proportional to the amount of phosphorus ingested and to the systemic manifestations of the poisoning. Peripheral vascular collapse and ventricular fibrillation are manifestations of grave significance, with early death from the direct effect of the poison. It seems plausible to assume that death follows a definite pattern with failure of the circulation as the most important governing factor. Serial electrocardiograms are indicated in every instance since transitory alterations frequently appear even among those who recover. This procedure may in some instances represent a valuable aid in the prognosis of this form of intoxication.

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## SUMMARIO IN INTERLINGUA

### Le Alterationes Electrocardiographic in Acute Invenenamento in le Homine

Un analyse del constatationes electrocardiographic in 55 patientes—representante un total de 59 essayos de suicidio per phosphoro jalne—revelava significative alterationes in 33 casos. Istos consisteva de prolongation del intervallo QT, alterationes del undas ST e T, e anormalitates de rhythmo e de bassessa de voltage in le complexos QRS. Registrationes de anormalitate marginal esseva trovate in 3 casos additional. Le incidentia del anormalitates electrocardiographic esseva directemente proportional al quantitate de phosphoro ingerite e al manifestationes systemic del invenenamento. Collapso vascular peripheric e fibrillation ventricular es manifestationes de grave signification, con morte precoce ab le effecto directe del veneno. Il pare plausibile supponer que le morte occurre secundo un definite schema de eventos, con disfallimento del circulation como le plus importante factor dominante. Electrocardiogrammas serial es indicate in omne caso, proque alterationes transitori occurre frequentemente mesmo inter illos in que le patiente se restabli. Iste mesura representa in certe casos un utile adjuta in le prognose de iste forma de intoxication.

# CORRECTION OF ERRATIC RESPONSE TO HYPNOTICS IN ELDERLY PEOPLE

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(From the Methodist Home for the Aged, Philadelphia, Pennsylvania)

It is a common observation that hypnotics may cause erratic action in the elderly patient and in children. Excitement, confusion, and stimulation may occur instead of the desired sleep. One possible explanation is that the erratic effect is related to interference with the highly integrated cortical control functions prior to the intended hypnotic action on the periventricular sleep centers in the brain. Such an interference is likely to be manifested more readily when the cortical function is not yet fully established, as in the young, or when it is beginning to fail, as in the old and presenile. If this assumption is correct, the undesirable excitation phase might well be reduced or eliminated by the addition of a tranquilizer. The latter could offset the loss of cortical personality control temporarily induced by the hypnotic. We have tested this in a group of truly old patients. The results are presented in the following report.

**Materials and Methods.** PATIENTS. The Methodist Home for the Aged in Philadelphia is a place of residence for approximately 250 aged persons for the remainder of their lives. It proved to be ideal for this type of study.

Since each guest is assured adequate care until he dies, worries about the future are minor. Otherwise, all of the insecurities seen in the elderly person are manifested here. Depression, confusion and anxiety are frequent, and not a day goes by without several people complaining of inability to sleep. In this group, particularly with the high incidence of cerebral vascular disease, psychotherapy and the like are impractical. Consequently, there is a frequent need for hypnotics at night.

The study was carried out on 52 patients who complained of inability to sleep. The youngest studied was 72; the oldest 97. A total of 168 records were kept on the 52 patients, each record covering a 24-hour period.

DRUGS. Three separate preparations were used. The first was a tablet containing 100 mg. of secobarbital; the second was an identical tablet containing 60 mg. of secobarbital and 100 mg. of phenyltoloxamine*; the third was a placebo.

*Secobarbital* was chosen for two reasons. First, it is one of the most commonly prescribed hypnotics. Second, its rapid action makes it suitable for study of the *early* effects of barbiturates.

*Phenyltoloxamine* was used in the combination tablet as the tranquilizing moiety. It is an antihistaminic of the diphenhydramine, Benadryl type with well documented tranquilizing action and absence of hypnotic action in the dosage employed (DiMascio and Rinkel[2], Klerman *et al.*[3], Sainz[4]). As it potentiates barbiturates (Avakian[1]), the secobarbital dosage in the combination was reduced from 100 mg. to 60 mg.

Comparison with placebo was necessary, as even an inert substance will produce a certain amount of improvement merely by the power of suggestion.

METHOD. A strictly alternating basis was followed. The tablets were identical and coded so that the attending personnel did not know which drug was being given. Only those patients who complained of an inability to sleep were included in the study. At half-hour intervals after administration of the drug each patient was observed by the physician on service and records kept with regard to the presence or absence of sleep, restlessness, thrashing around, noisiness, and coherence. On the following morning the same physician evaluated each patient for evidence of headache, drowsiness, nausea, nervousness, visual disturbance, paresthesias, and any other indication of "hangover." Each person's opinion of his night's sleep was also recorded. After

*Supplied as Hyptran by Wampole Laboratories, Stamford, Conn.

completion of the 24-hour record it was filed and at the conclusion of the investigation the code numbers of the drugs were broken and the results compared.

**Results.** Table 1 shows the data covering the time of falling asleep. Thirty-eight patients (74%) receiving secobarbital were asleep within 90 minutes, and 14 (26%) were not. Of the latter group, several dropped off to sleep sometime later during the night, but this cannot be considered as sleep induced by the barbiturate. In the same time period (90 minutes), 48 patients (92%), who received the combination were asleep, and 4 (8%) remained awake. Of the patients who received the placebo, 34 (65%) were asleep within 90 minutes; 18 (35%) remaining awake. The differences among the three groups are statistically significant.

The average length of sleep induced by secobarbital (100 mg.) was 5½ hours; by secobarbital (60 mg.) plus phenyltoloxamine it was 7¼ hours; and with the placebo it was 5 hours.

Table 2 shows the patient's opinion of sleep after use of the various drugs. Administration of a hypnotic decreased the incidence of unsatisfactory sleep. Six (12%) of those who received secobarbital had unsatisfactory sleep, and only 2 (4%) of those who received the combination tablet felt that they had not slept well.

Table 3 shows the incidence of initial stimulation and excitement. Secobarbital produced reactions that were considered as stimulation in 9 (17%) of the patients. The combination tablet produced such reactions in only 4 (8%), and 8 (16%) of those who received placebos were restless or excited. One might conclude that secobarbital is not much more likely to cause excitability than an inert substance. Nevertheless,

TABLE 1.—FALLING ASLEEP

| | *Secobarbital 100 mg.* | | *Secobarbital 60 mg. plus Phenyltoloxamine 100 mg.* | | *Placebo* | |
|---|---|---|---|---|---|---|
| | *No.* | *%* | *No.* | *%* | *No.* | *%* |
| Asleep in 30 minutes | 28 | 54 | 33 | 63 | 19 | 36 |
| Asleep in 30–60 minutes | 7 | 14 | 13 | 25 | 10 | 19 |
| Asleep in 60–90 minutes | 3 | 6 | 2 | 4 | 5 | 10 |
| No sleep | 14 | 27 | 4 | 8 | 18 | 35 |

TABLE 2.—PATIENT'S OPINION OF SLEEP

| | *Secobarbital 100 mg.* | | *Secobarbital 60 mg. plus Phenyltoloxamine 100 mg.* | | *Placebo* | |
|---|---|---|---|---|---|---|
| | *No.* | *%* | *No.* | *%* | *No.* | *%* |
| Sleep satisfactory | 46 | 88 | 50 | 96 | 29 | 57 |
| Sleep unsatisfactory | 6 | 12 | 2 | 4 | 23 | 43 |

the fact remains that in 17% of these elderly persons secobarbital either stimulated or failed to relieve existing excitation from whatever other cause. The addition of phenyltoloxamine to the barbiturate decreased this incidence by half.

addiction or habit formation developed. A complete blood count and urinalysis were performed on all patients at the conclusion of the study and all were within normal limits.

**Summary and Conclusions.** The administration of hypnotics may cause

TABLE 3.—TYPE OF SLEEP

| | *Secobarbital 100 mg.* | | *Secobarbital 60 mg. plus Phenyltoloxamine 100 mg.* | | *Placebo* | |
|---|---|---|---|---|---|---|
| | *No.* | % | *No.* | % | *No.* | % |
| Restless, noisy, excited, and the like | 9 | 17 | 4 | 8 | 8 | 15 |

TABLE 4.—CONDITION OF PATIENT THE FOLLOWING MORNING

| | *Secobarbital 100 mg.* | | *Secobarbital 60 mg. plus Phenyltoloxamine 100 mg.* | | *Placebo* | |
|---|---|---|---|---|---|---|
| | *No.* | % | *No.* | % | *No.* | % |
| Drowsiness, "hangover" | 9 | 17 | 6 | 12 | 7 | 13 |

The incidence of "hangover" on the following day is shown in Table 4. With secobarbital 100 mg., despite its relatively short action, headache, nausea, drowsiness, or other late symptoms were reported in 9 (17%) of the patients. With the secobarbital-phenyltoloxamine combination this incidence, 6 patients (12%), was not higher than that incurred while the patients were on placebo (13%). No case of either erratic excitation in aged patients. The addition of phenyltoloxamine to secobarbital permits a lowered dosage of the hypnotic; curbs the excitatory phase; allows for a prompt, more satisfactory sleep; and lessens the incidence of hangover the following day. The combination of these drugs in a single tablet is a safe and effective hypnotic for the elderly, and is without significant side-effects.

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# PROGRESS
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## PEDIATRICS

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## MATERNAL-FETAL RELATIONSHIPS IN NORMAL AND ABNORMAL THYROID DEVELOPMENT OF THE NEWBORN*

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IMPRESSIVE advances in the knowledge relating to the interrelationships of normal maternal and fetal thyroid function have been made in recent years. Similarly a number of factors, genetic and acquired, which alter these interactions with resulting thyroid abnormality in the newborn, have been elucidated. The purpose of this paper is to present a pertinent review of these contributions.

THYROID FUNCTION IN PREGNANCY. The oldest recognized clinical sign which prompted earlier investigators to suspect that there was an alteration in the thyroid function during pregnancy was enlargement of the thyroid gland[67, 89, 151]. Reports of alterations in other parameters of thyroid function during pregnancy have followed these early clinical observations.

An increase in the basal metabolic rate during pregnancy was first described by Magnus-Levy[86]. Numerous

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investigators over the past 50 years have confirmed these observations[46]. An elevation of the circulatory level of thyroid hormone, serum protein bound iodine (PBI) and butanol extractable iodine (BEI), seems to be characteristic of pregnancy[135].

Alterations in the $I_{131}$ uptake by the thyroid are controversial. Elevated uptakes with a more rapid conversion to a protein bound form of the incorporated iodine have been reported[47,58,110,124]. However, other investigators have pointed out that in humans and in experimental animals the $I_{131}$ uptake during pregnancy is elevated only as compared to the values obtained during the puerperium and that the low thyroidal postpartum uptake may have been due to an increased accumulation of $I_{131}$ by the mammary glands[32,74]. Furthermore the recent findings of Iino and Greer[74], in the rat, indicated there is no increased utilization of thyroid hormone during pregnancy, since the amount of thyroxine required to prevent propylthiouracil-induced goiter or to depress radioiodine uptake was similar in both pregnant and nonpregnant rats.

Persani *et al.*[119] have recently reported a marked elevation of thyrotrophic hormone (TSH) levels in pregnancy.

FACTORS AFFECTING PLACENTAL TRANSFER OF PITUITARY AND THYROID HORMONES. *Protein Binding of Thyroxine.* An explanation for the paradoxical finding in normal pregnancy of an elevated protein bound iodine, without evidence of hyperthyroidism, was afforded by the demonstration in extracellular fluid of specific protein moieties which reversibly bind thyroxine. At least three proteins which bind thyroxine have been identified by electrophoretic techniques in several alkaline buffers: Thyroid binding globulin (TBG) with an electrophoretic mobility between alpha 1 and alpha 2 globulin, a pre-albumin fraction (TBPA) and albumin. TBG accounts for most thyroxine transport at physiological concentrations. Albumin normally has little thyroxine associated with it and is therefore of little significance[75,127,140,154]. The role of TBPA has been questioned since it is sensitive to buffer composition *in vitro* and may not correspond to the *in vivo* situation[26]. So far, quantitation has been achieved by indirect methods with results expressed in terms of concentration of binding sites rather than of protein. The nature of the binding is such that thyroxine on one site is readily exchangeable with thyroxine on other sites or with added thyroxine[127,140]. Although the concentration of free thyroxine is too low to be measured directly (with an estimated relative value of 0.06% of total thyroxine[127]), it is believed to be in equilibrium with the bound thyroxine. Most methods which reflect the thyroxine-binding capacity of serum protein, and presumably free thyroxine, depend on the concentration of unoccupied binding sites. Measurement of the fractional uptake of radio-triiodothyronine by erythrocytes[61,62] or ion exchange resins[97] from plasma is commonly used.

Species differences in thyroxine binding proteins (TBP) have been found in a number of laboratory animals[127]. The monkey has TBP similar to man, whereas the rat has only one peak in the albumin zone. The qualitative alterations in the rabbit are especially noteworthy[102,103,114]. The TBP of adult rabbits is found between albumin and alpha 1 globulin. In the 25-day-old fetus, binding activity is in a single peak between the alpha 2 and beta globulin, and in a mixture of adult and fetal TBP, the latter has a binding power one third that of the adult TBP. By 28 days they are nearly equal. In

man, the maternal-fetal partition of serum thyroxine can not be studied *in vitro* because TBP in the human fetus is indistinguishable from that in adults. However, the thyroxine binding capacity of TBP in serum of the human fetus at the 15th week is much lower than in maternal serum, and to this extent findings in rabbits apply to humans[114].

Alterations in thyroxine binding by serum protein was first looked for in pregnant women because of the elevated PBI in the absence of hyperthyroidism. TBG increases very early in pregnancy and remains elevated briefly into the puerperium. A rise to 2½ times normal has been found as early as the second month of gestation[39,128,152].

In keeping with the TBG measurements were the findings of a depressed erythrocyte and ion exchange resin uptake of radiotriiodothyronine[61,62,63,152], and of a decreased fractional rate of dialysis of radiothyroxine[27]. Of interest are the observations that women with inevitable abortion do not have an elevated PBI and TBP capacity characteristic of normal pregnancy[39,87,140].

Ingbar has demonstrated that there is not an increase in TBPA during pregnancy in the human, but that after delivery there is a fall. This decrease in TBPA seems to occur with any stressful situation such as surgery or febrile illnesses[75,76]. Increases in PBI and TBP similar to those found in normal pregnancy are induced by administration of large doses of estrogens to normal subjects and to patients with treated myxedema and with treated hypopituitarism[40,41,43,62]. These findings suggested that increased TBG capacity in pregnancy is a result of estrogen secretion and that the increased PBI is secondary to the change in TBG. Elevations in thyroxine-binding protein capacity have also been found in hypothyroidism[129] and in liver disease[160]. Familial instances of elevated serum PBI levels with increased TBG capacities have been described in presumably normal individuals[9,48].

A decreased PBI concentration and TBG capacity have been observed in a normal man[153], and in individuals receiving androgen[44] and salicylate[7]. The latter was demonstrated to interfere with binding of thyroxine[28]. The opposite of the paradox seen in normal pregnancy exists in nephrosis, in which the absence of myxedema with a low PBI is attributed to the finding of low thyroxine-binding activity of TBP which may be associated with the profound renal losses of plasma protein[130].

During pregnancy studies in humans, the TBG capacity in umbilical cord blood and blood of newborn infants was found to be increased compared to the TBG capacity of normal adults, but was not as high as in the mother at term[39,128,136]. Marks *et al.*[90] have observed in full-term and premature newborns an increased erythrocyte uptake of radioiodine-labeled triiodothyronine which falls to the adult range at 6 to 9 weeks of age. Increased uptake of $T_3$ is even more pronounced and prolonged in prematures. In full term infants Spafford *et al.*[150a] found that the $T_3$ uptake increased to a peak on the 2nd day of extrauterine life.

The significance of protein binding of thyroxine in regard to maternal transfer of thyroxine to the fetus, and ultimately to peripheral metabolism of the hormone in each, appears to be related to the rate-limiting influence which accompanies the alterations cited.

*Placental Barrier.* The role of placental transfer of pituitary and thyroid hormones from the maternal to the fetal circulation and its relation to fetal thyroid development has received con-

siderable attention. In 1952, Peterson and Young[120] demonstrated in thyroidectomized pregnant guinea pigs that neither endogenous nor exogenous TSH crossed the placenta to the fetus. However, propylthiouracil given to the pregnant animal induced fetal thyroid hyperplasia that could be inhibited by concomitant administration of thyroxine, indicating placental transfer of both substances. Knobil and Josimovich[80] and Sobel *et al.*[141] similarly have shown that thyroxine and triiodothyronine crosses the placenta in rats but these studies give no indication of the rate of transfer. Nataf *et al.*[106] found that within 2 hours after an injection of radiotriiodothyronine into pregnant rats, the concentration of radiotriiodothyronine in the fetal serum was nearly in equilibrium with the maternal serum. The concentration of radiothyroxine and triiodothyronine injected into guinea pigs in late pregnancy was much lower in the fetal serum after 4½ hours than that in the mother's serum[85]. These results indicate a marked species difference in placental transfer of thyroid hormones. If the placenta is impermeable to TBP but permeable to free thyroxine then only a small proportion of circulating hormone will be available for exchange. The partition of thyroxine between mother and fetus would depend on the relative concentration and affinities of thyroxine-binding proteins in the maternal and fetal serum. Direct support for this hypothesis was provided by the observations made in rabbits in which the rise in the binding power of fetal serum occurring with increasing age leads to an apparent increase in placental permeability to thyroid hormone[56,103].

The placental transfer of radiothyroxine to the human fetus at term in the first few hours after injection was found by Grumbach and Werner[54] to be slow, but relatively high serum concentrations of radiothyroxine were reached with fetal/maternal ratios ranging from 0.13 to 0.48, 18 to 169 hours after injection. Triiodothyronine appeared to pass more rapidly. Myant[104] found the passage of thyroxine to the human fetus between 11 to 25 weeks to be very slow, the fetal/maternal ratio averaging 0.058, 14 to 53 hours after injection. There was no tendency for the fetal/maternal ratio to increase during this period of pregnancy. The passage of triiodothyronine was again more rapid. The suggestion was made that the somewhat faster rate of placental transfer of triiodothyronine in man and rabbit may be due to the fact that it is not as firmly bound to TBG as thyroxine. The finding of a much lower thyroxine-binding capacity in the serum of the human fetus at 15 weeks than in the maternal serum correlates with the low placental transfer rate of thyroxine and triiodothyronine in early pregnancy. As previously stated, it is not possible to distinguish human fetal TBG from adult TBG[114].

The assumption that thyroid hormone can cross the placenta in both directions is basic to the concept of a competition for thyroxine between two binding proteins separated by the placental barrier permeable to free thyroxine. Studies with radiothyroxine injected into the fetus have been inconclusive primarily because of the large difference in fetal and maternal blood volumes[56,114].

In spite of the many metabolic functions of the placenta, other than allowing passage of iodide, thyroxine and triiodothyronine[54,104], the placenta does not directly contribute to the maternal or fetal serum concentration of thyroid hormones. Human placental tissue incubated with radioactive iodide failed to organify iodide nor did it deiodinate diiodotyrosine or thyroxine[169].

THE DEVELOPMENT OF THE FETAL THYROID. Embryologically, the thyroid gland is a non-paired derivative of the primitive pharyngeal floor and most human embryologists are of the opinion that, in man, it follows the typical vertebrate pattern[59]. The cytological changes occurring in the thyroid in human embryos are well established, thyroid cells appear around the third fetal week and the follicles and colloid form around the thirteenth or fourteenth fetal weeks[111].

Because of the selective and special way in which the thyroid gland utilizes iodine in the biosynthesis of thyroid hormones, Trunnell and Wade[156] postulated the existence of an "embryonic stairway" up which the primitive thyroid glands must come to reach "maturity." Their work demonstrated that there is a chronology in the synthesis of iodinated compounds by the chick embryo thyroid, beginning with the ability to concentrate iodide at 7 to 7½ days, and to synthesize moniodotyrosine (MIT) at 8½ days, diiodotyrosine (DIT) at 9½ days, and thyroxine at 9¾ days. Pickering and Kontaxis[122] demonstrated in monkeys that chemical growth paralleled physical growth of the gland. Hodges *et al.*[68] and Chapman *et al.*[23] have shown that the human fetal thyroid is capable of concentrating radioiodine between the third and fourth months of pregnancy. Yamazaki *et al.*[170], studying the development of thyroxine synthesis in the human fetus, concluded that iodide can be accumulated at or prior to 14 weeks but that only by 19 weeks is the fetal gland able to synthesize thyroxine and that by the twenty-second week the MIT/DIT ratios were those normally found in the adult thyroid. These findings tend to indicate that there is also a sequential development of hormonal biosynthesis in the human fetal thyroid which parallels the now accepted serial reactions by which the normal human thyroid gland synthesizes hormone: (A) Concentration of iodide by the gland from the blood; (B) Oxidation of the trapped iodide; (C) Binding of the oxidized iodide to tyrosine in thyroglobulin, first as MIT, then as DIT; (D) Coupling of the two molecules of DIT to form thyroxine, or one molecule each of DIT and MIT to form triiodothyronine[15,140].

The role that the maternal hormones, thyroid and thyrotrophic, may play in the normal or abnormal development of the thyroid gland has been partially elucidated by the following series of animal experimentations and by clinical observations. In guinea pigs[120] and dogs[22] it has been demonstrated that the removal of the maternal thyroid had no effect on the normal development of the fetal gland. Peterson and Young[120] concluded that maternal hypothyroidism did not induce hypertrophy of the fetal thyroid because either maternal TSH does not cross the placenta, or the fetal thyroid responds only to fetal TSH. Nikitovich and Knobil[109], working with the rat, confirmed the findings of Peterson and Young and further elucidated the role of maternal TSH by demonstrating that maternal TSH is not essential for the development of the fetal rat thyroid, since the offspring of hypophysectomized rats developed normal thyroid glands. In similar experiments, these and other investigators[80,109,120,141] demonstrated that thyroxine is capable of inhibiting fetal goiter development secondary to the administration of propylthiouracil to the mothers. Knobil and Josimovich[80] showed that, paradoxically, thyroxine is approximately two times more effective than triiodothyronine in suppressing fetal goitrogenesis in the rat, but less effective than triiodothyronine in inhibiting goiter formation in the mother.

The mechanism by which thyroxine inhibits fetal goitrogenesis is cleverly depicted by the work of Jost[79]. Using propylthiouracil-treated pregnant rabbits, he was able to inhibit fetal goiter formation by the *in utero* decapitation of the fetus, and thus established that fetal TSH is essential for hypertrophy of the fetal thyroid.

Observations on sporadic goiter of the newborn, to be discussed later, suggest that the human fetal thyroid is also under the control of the fetal pituitary. Although it appears that there is a definite correlation between fetal pituitary and thyroid development, there is no clear understanding of the requirements of the fetus for thyroid hormone. The early stages of growth and differentiation presumably take place in the absence of thyroid hormones, since maternal thyroxine appears to be unable to reach the fetus during this period and the fetal gland has not begun to function. However, there is a strong indication that in later fetal life the production and release of fetal thyroid hormone is essential. First, the gland is able to synthesize hormone after the 19th week. Second, an inability of the fetal gland to produce thyroxine, results in impaired development of the osseous and central nervous systems, even in offsprings of euthyroid mothers, indicating that placental transfer of thyroxine alone is not adequate to supply normal fetal requirements[4,38,165].

NEONATAL THYROID FUNCTION. Danowski *et al.*[33] were first to report the levels of serum protein bound iodine within the newborn period. Their results indicated that within 12 hours after birth the serum protein bound iodine of the infants is of the same order of magnitude as that present in maternal blood at time of delivery (8.3 ± 2.4 gamma %) with a gradual increase reaching a peak (12.0 ± 2.4 gamma%) by the 3rd day and persisting during the entire first week of life. These values are higher than the accepted standard values for adult euthyroid subjects. Man *et al.*[88], measuring thyroxine-like butanol extractable iodine (BEI) in maternal and cord blood, found that the values did not differ by more than 1.6 gamma % from each other; however, in 12 of 13 infants, 2 to 6 days of age, the BEI ranged between 7 and 11.7 gamma %. A subsequent report[123] confirmed these observations and demonstrated that the sharp increase in the level of BEI occurs during the 1st week of life, reaches its peak by the 5th day (mean 9.9 ± 2.1 gamma%), and returns to values found in cord blood (5.5 ± 0.94 gamma %) by the 18th to 20th days.

Studies of $I_{131}$ uptake by the thyroid of the newborn have yielded conflicting reports. Van Middlesworth[158] found the mean value for 7 newborns aged 2 to 3 days to be 69.7%. Subsequent studies[91,112] using more refined techniques have failed to demonstrate abnormal elevations in the $I_{131}$ uptake by the newborn's glands.

While it is possible that technique could account in part for these discrepancies, the age of the newborn may be more significant. In monkeys the $I_{131}$ uptake during the first 24 hours of life is between 60 and 90% and decreases by the 5th day[123]. In addition, close examination of the combined data on $I_{131}$ uptake in the newborn reported by Martmer *et al.*[91] and Ogborn *et al.*[112] reveals that only two full-term infants and four prematures under 3 days of age were studied, while Van Middlesworth's 7 patients were all 3 days of age or younger. The studies on PBI and BEI, mentioned above, have all emphasized the progressive increase in these values during the first week of life with a peak level occurring after the 3rd and 4th day of life. It is quite

conceivable that an increased affinity of the gland for iodine exists only until the peak levels of circulating thyroid hormones are reached.

In the newborn period the elevation in the levels of PBI and BEI in the absence of overt signs of hyperthyroidism cannot be explained by alterations in the thyroxine-binding properties of plasma proteins as in pregnancy. Although the maternal and cord blood BEI levels are the same, the TBP capacity in cord blood is less than that found in the mother[39,136]. Furthermore, Marks *et al.*[90] have recently demonstrated elevated values for the erythrocyte uptake of radiotriiodothyronine ($T_3$) and, as they point out, if the increased PBI and BEI levels were solely secondary to an increase in TBP capacity, the $T_3$ uptake should be low. They concluded that these findings indicated a true increase in thyroid function.

Related to the foregoing consideration of factors that influence fetal thyroid function, an alternate explanation is proposed. A significant role in thyroxine metabolism of the fetus and newborn may be its enterohepatic circulation. In experimental animals and man, the liver has been shown to accumulate and secrete glucuronide and sulfate conjugates of thyroxine in the bile which enters the gastrointestinal tract where hydrolysis of the conjugates occurs[11,131]. Free thyroxine is then reabsorbed into the circulation.

In man, the enterohepatic circulation of thyroxine is relatively slow in contrast to the rat, however, 10 to 30% of the circulating organically bound iodine is normally excreted in the feces[13,105,159]. In the rat marked increases in intestinal losses of hormone with subsequent goitrogenesis are induced by feeding soya flour or cellulose[8,159]. A similar phenomenon may play a part in the etiology of goiters in some children receiving soy bean milk[73,161].

Vannotti and Beraud[160] and Beraud[11] have found in liver damage due to infectious hepatitis an increase in serum PBI without evidence of hyperthyroidism. This high level of thyroxine is attributed to the slow turnover due to decreased glucuronide conjugation. The associated increase in TBP capacity was believed to explain the normal basal metabolism and again indicated that free thyroxine is the active form. In normal subjects serum contained only free thyroxine, whereas bile contained free thyroxine and glucuronic acid conjugates of thyroxine. In infectious hepatitis the bile contained free thyroxine or only traces of glucuronide conjugates. In obstructive jaundice glucuronide conjugates were present in the serum. Similar results were obtained in rats with experimental liver damage.

The characteristically reduced ability of the fetal neonatal liver to synthesize glucuronic acid conjugates produces physiological and abnormal alterations in metabolism of a variety of endogenous and exogenous products in the neonatal period[42]. Thyroxine-like bilirubin is excreted in the bile as glucuronide and sulfate conjugates. The fact that thyroxine and bilirubin seem to accumulate during the first few days of life tends to indicate that not only is the system of conjugation immature, but that there is also competition between these two, and probably other metabolites for the same system, accounting for their retention in the circulation.

Decreased removal of circulating thyroxine, secondary to decreased hepatic conjugation, could account for the high PBI and BEI levels. Furthermore, the increased circulating thyroxine brought about by such a mechanism would tend to saturate the plasma thyroxine binding system and produce the elevated erythrocyte $T_3$ uptake seen in newborns. However, it would not explain

the absence of signs and symptoms of hyperthyroidism. Possible explanations could be the production or retention of a butanol-soluble material similar to thyroxine but metabolically less active, or decreased peripheral utilization of thyroid hormone. There is no evidence to support the former. In favor of the latter are the observations of Moncrieff[98] and Stevenson *et al.*[150] that premature infants could tolerate large doses of thyroid, up to 180 mg. of thyroid or 0.2 mg. of thyroxine, daily for several weeks before mild toxic symptoms appeared.

CONGENITAL ABNORMALITIES OF THE THYROID. *Non-goitrous Cretinism:* Athyrotic Cretins. The most common form of sporadic congenital hypothyroidism is the athyrotic type[165]. Advances in diagnostic techniques have made possible the differentiation of cretins with inborn errors of thyroid hormone metabolism and those with ectopic or non-functioning glands, formerly classified in the athyrotic group, but they have failed to explain the etiology of congenital absence of the thyroid. Since there are no studies of spontaneous or experimentally produced athyrotic animals, hypotheses regarding athyrotic newborns have been made primarily from clinical observations.

Aplasia and hypoplasia of the fetal thyroid have been regarded as embryonic defects of the gland. Dorff[38] was the first to emphasize this possibility from his observation of a case of non-goitrous cretinism in one of heterozygous twins. He concluded that a fetal influence from the mother was unlikely.

Very little is known of the role that intrauterine infections may play in thyroid aplasia; however, cases of congenital toxoplasmosis associated with athyrotic cretins have been reported[1,5]. Whether this represents chance rather than true association is not known. The possible hazard of thyroid destruction of the fetus following the administration of radioactive iodine to pregnant women after the twelfth week of gestation has been emphasized[23,68] and implicated in case reports of athyrotic cretins[126].

Lack of fetal TSH as the cause for failure of the fetal thyroid to develop has been postulated[70]. To the contrary, elevated TSH levels have been observed in athyrotic cretins[2,19,36,51].

A familial incidence is infrequently associated with this entity. Childs and Gardner[25] reported 2 affected siblings in a series of 88 athyrotic cretins, and Bernheim *et al.*[12] only one in 34. Wilkins[166] commented that he has only seen one pair of siblings among 150 cases. Neel *et al.*[107] reported none among 109 liveborn siblings of athyrotic cretins. Ainger and Kelley[6] described 3 cretinous siblings and Federman *et al.*[45] 2 in whom $I_{131}$ uptake studies revealed no evidence of thyroid tissue. However, subsequent studies using TSH stimulation prior to $I_{131}$ uptake were not carried out in these patients.

The markedly increased consanguinity rate seen among parents of the congenital hypothyroids due to enzymatic defects is, by contrast, only slightly more frequent in the athyrotic group than in the general population[107]. However, a sex ratio difference is consistently reported for the athyrotic type, with females having a significantly higher predisposition for this anomaly than that seen in goitrous cretins[12,52,107].

The presence of abnormal thyroid function in the immediate relatives of these patients is controversial. Childs and Gardner[25] believe that there is an increased frequency of clinical thyroid disease among the parents of sporadic cretins. Bernheim *et al.*[12] measured the $I_{131}$ uptake in 35 parents and 24 siblings and found the average to be 54 and 57% respectively in contrast to a

37% average value in the control group. These values were interpreted to signify a metabolic abnormality. Neel *et al.*[107] found 4 goitrous mothers and no goitrous fathers among 32 sets of parents of athyrotic children and concluded, after comparing this group with the enzymatic defects, that this did not represent a significantly high incidence of thyroid disease. After a comprehensive review of the genetic aspects of athyrotic cretins, Neel *et al.*[107] advanced the hypothesis that thyroid agenesis may be the result of segregants (phenodeviants) as postulated for other human congenital malformations[108].

*Role of Phenothiocarbamide Nontasters.* Shepard *et al.*[137] have recently focused attention on a new approach to the study of a possible mechanism for congenital athyrosis, the role of phenothiocarbamide (PTC) tasters. Fox[49], in 1931, found that a certain percentage of Europeans could not taste PTC. Blakeslee[14] demonstrated that the inability to taste was inherited as a Mendelian recessive characteristic (genotype "tt"). Harris and Kalmus[64] pointed out that the specific chemical group involved in this defect was common to antithyroid substances (thiocarbamides). Subsequently they found a high incidence of non-tasters in individuals with non-toxic nodular goiters and thought that this might be related causally[65]. Shepard *et al.*[137] have recently shown that there is also an increased incidence of phenylthiocarbamide non-tasters among congenital athyrotic cretins, their parents and siblings. Based on these observations they advanced the following hypothesis: "A fetus who is a non-taster may be susceptible to embryonic thyroidectomy by goitrogens ingested by the mother. A non-taster may have an inability to convert thiocarbamide goitrogens to an inactive form and thus be more sensitive to their biological effects, which could lead to destruction of the early differentiating thyroid." As they pointed out, a defect of this hypothesis is the lack of explanation for the presence of normal non-tasting siblings. It should also be noted that previous reports of the effects of goitrogens administered during pregnancy to humans and experimental animals have demonstrated hypertrophy rather than atrophy of fetal thyroid.

SUBLINGUAL THYROID. Horst and von Harnach[69] first demonstrated the uptake of $I_{131}$ by sublingually retained thyroid tissue in non-goitrous cretins. Previously this type of congenital hypothyroidism was classified with the athyrotic group. Andersen[4] has recently summarized the cases reported in the literature up to 1960 and added 13 of his own. The cause for the sublingual retention of thyroid tissue is unknown but it is believed to be a different embryonal defect with failure of descent or incomplete migration of the fetal thyroid[3]. In Andersen's series the prognosis for normal mental development in this group was considerably more favorable than in cretins without demonstrable thyroid tissue.

*Role of Maternal Thyroid Autoimmunization.* The fascinating new concepts of thyroid disease associated with various circulating thyroid autoantibodes have been the subject of a number of recent reviews[16,127,132,139]. The studies of Blizzard *et al.*[17] relating maternal autoimmunization to thyroid as a probable cause of athyrotic cretinism are particularly pertinent. A battery of methods was used to detect circulating, agglutinating, complement-fixing, and precipitating thyroid antibodies in the serum of mothers of cretins. Eleven of 67 sera, or approximately 16%, gave positive tests by at least one of the 5 antibody techniques employed.

Antibodies were demonstrated in 5 of the newborn infants whose mothers

had antibodies. (In a previous study Beierwaltes *et al.*[10] found positive agglutinating antibodies in 3 of 20 mothers and none in cretins). Four of these mothers had active or proved history of thyroid disease. In 2 mother-and-infant pairs, the offspring were cretins; the other 3 were normal. One of these mothers developed spontaneous myxedema 18 months before birth of an athyrotic cretin. The other had a history of thyroiditis at 6 years of age, was subsequetly hypothyroid and later gave birth to 2 and possibly 3 cretins. There were varying degrees of damage to the thyroids of these infants with a suggestion of some protective effect of substitution therapy given to the mother[142]. The two mothers who produced cretins had a cytoxic agent for thyroid cells in tissue culture in addition to circulating antibodies. Some investigators have concluded that the presence of a circulating cytoxic factor correlates better with clinical and experimental findings in autoimmune thyroid disease than the commonly measured circulating thyroid antibodies[77,125,132].

There was rapid disappearance of the antibodies from the serum of the cretins and normal infants during the first few months of life; this fact would tend to explain the presence of antibodies in only one of 50 athyrotic cretins in this study who were over 4 months of age. Two of 8 of the cretins under 4 months of age had demonstrable antibodies. Since antithyroid antibodies are gamma globulins, it was not surprising that their disappearance correlated with the time at which the lowest levels of gamma globulin in the serum are reached in the infant[20]. Even though it has been shown that the human fetal thyroid contains thyroglobulin antigenically indistinguishable from adult thyroglobulin[134], the release of this antigen in the newborn period from a damaged thyroid would not be expected to induce autoantibody production since newborn animals generally accept antigenic proteins as normal proteins[21].

The incidence of cretinism in the offspring of pregnant women with thyroid antibodies was not definitely determined, but at least 13 of 18 offspring available for follow up from the control pregnant group with antibodies had no clinical thyroid disease. However from this study it can be concluded that when antithyroid antibodies cross the placenta, normal children or athyrotic cretins may be born depending on the amount of placental transfer of the "thyrocytoxic" factor which is associated with the antibodies. The presence or history of thyroid disease in the mother with thyroid antibodies increased the likelihood of the cytoxic factor also being present.

Of interest is the study of Hall *et al.*[37] in which a markedly increased frequency of circulating thyroid antibodies in relatives of patients with autoimmune thyroid disease was discovered. Twenty-two of 39 siblings had circulating thyroid antibodies. Eleven of the 22 had no thyroid disorder. They suggested that environmental factors in autoimmune thyroid disease are either not implicated or operate only against a background of genetic susceptibility. In view of the high proportion of relatives without clinical thyroid abnormality, but with circulating antithyroid antibodies, the significance of autoimmunity in the pathogenesis of thyroid disease was again questioned.

CONGENITAL GOITROUS CRETINISM. *Inborn Errors of Thyroid Hormone Synthesis and Metabolism.* In recent years a number of genetically determined inborn errors in thyroid hormone synthesis have been described. Included are five specific defects in synthesis and

others that are probably inherited defects in synthesis, transportation and metabolism. There are several recent reviews of the historical background and evidence on which biochemical anomalies in each defect have been classified and these will not be repeated herein[15,29,92,143,155]. Table 1 lists the specific defects in thyroxine synthesis, with reference to the time of development of goiter or hypothyroidism, or both, in each.

TABLE 1.—INBORN ENZYMATIC DEFECTS IN THYROID HORMONE SYNTHESIS

| *Defect* | *Appearance of Goiter or Hypothyroidism, or both** | | |
|---|---|---|---|
| 1. Trapping defect | CHo–G[144] | CGHo[45] | |
| 2. Inability to organically bind iodine | CHo–G[32,55,117,145] | CG–Eu[30] | G–Eu[30,99] |
| 3. Inability to couple iodotyrosine to produce iodothyronine | CHo[162] | CHo–G[101] | |
| 4. Inability to dehalogenate iodotyrosine | CGHo[146,147] | CG–Ho[93] | G–Eu[147] |
| 5. Abnormal formation or release of abnormal iodinated proteins | CHo–G[20,34] | Ho[163,164]GHo[37] | CGHo[163] |

*CG–Eu Congenital goiter, euthyroid
CGHo Congenital goiter with hypothyroidism
CG–Ho Congenital goiter, hypothyroidism developing later
Eu–G Euthyroid goiter developing in childhood or adolescence
CHo–G Congenital hypothyroidism with delayed goiter development
Ho Hypothyroidism without goiter
GHo Goiter with hypothyroidism, not congenital

A probable defect in the protease or peptidase enzyme systems responsible for release of thyroxine from thyroglobulin has been suggested in 2 goitrous hypothyroid individuals reported by Hamilton *et al.*[60]. Their glands contained normal amounts of thyroxine as determined by chemical analysis. Hypothyroidism developed at birth and between one and 2 years.

Defects of thyroid hormone transport in the blood, including excessive and decreased thyroxine binding proteins, may also represent inborn errors of metabolism. In a family reported by Beierwaltes and Robbins[9], two asymptomatic members (father and one of 2 children) were found to have an elevated PBI, elevated TBG capacity, and decreased erythrocyte uptake of $T_3$. Similar abnormalities in 4 individuals in 3 generations were found in the family studied by Florsheim *et al.*[48]. These studies support the thesis that TBG levels may be genetically determined; however, the exact mode of transmission is not yet clear.

Tanka and Starr[153] have reported opposite findings in a normal adult male with a PBI of 3.0 μg. per 100 ml. and absent TBP. Ingbar[75] has recently reported a similar patient without hypothyroidism who had a PBI of 2.0 μg. per 100 ml., normal TBPA, and absent TBG. It has not been proven that these represent genetic defects.

A possible defect in the enzymes responsible for degrading thyroxine to triiodothyronine was postulated by Hutchison *et al.*[71] as the basis for hypothyroidism in a 4-year-old girl with a sublingual thyroid. This patient responded only partially to desiccated thyroid but dramatically to triiodothy-

ronine. Further evidence to support this thesis has not been presented.

The five apparently distinct defects in thyroid hormones synthesis have a common result, namely, inadequate production of effective thyroid hormone with compensatory goiter formation. The low circulating levels of thyroxine stimulate the anterior pituitary to produce more TSH which in turn causes hyperplasia and hypertrophy of the thyroid[29,92,143,155]. From the wide variation in time of development of hypothyroidism and goiter, it is likely that the enzymatic defects in synthesis occur in variable degrees of severity. If severe, congenital goitrous cretinism results; if mild, a "simple" sporadic goiter develops in later life, perhaps in response to other factors such as increased metabolic demands, iodine deficiency, or exogenous goitrogens[30,92].

The familial tendency and occurrence of consanguinity in goitrous cretinism, or hypothyroidism in the absence of iodide deficiency, were noted by Osler in 1897[113] and have been fully confirmed by subsequent investigators[72,83,147,167]. Genetic studies indicate that the dehalogenase defects[94,147] and defective organification of iodine[50, 117,155] are transmitted by a single recessive autosomal gene. The genetic significance of the frequent association of the latter defect with deafness has not been established[92]. The genetics of other defects have not been worked out, but the familial incidence strongly suggests that they also have a genetic basis.

*Reversibility of an Enzymatic Defect of Thyroxine Synthesis.* An interesting new concept of the possible reversibility of an enzyme defect has recently been proposed by Zondek *et al.*[171,172]. Three siblings with goitrous cretinism with an apparent inability to organify iodine (abnormally high $I_{131}$ uptake during the first few hours after administration, with a subsequent drop to abnormally low levels and low serum PBI) were treated with short termed administration of massive doses of active thyroid substances, "stosstherapy" (90 mg. of triiodothyracetic acid or equivalent doses of desiccated thyroid within 6 to 9 days).

In each instance "stosstherapy" resulted in a protracted clinical remission including complete or partial regression of the goiter lasting 6 to 7 months. Studies of thyroid function performed during the therapy-free remissions revealed normal PBI levels and a normal or elevated $I_{131}$ uptake, indicating that the thyroid was able to organify iodine into a biologically active form that could maintain a euthyroid, goiter-free state. Similar therapy was ineffective against 2 cases of both pituitary myxedema and primary myxedema. It was concluded that the effect of "stosstherapy" depended on the mode of administration and not the nature of the thyroid compound employed. It was postulated that "stosstherapy" acts as a trigger-mechanism through which the disordered interaction between specific thyroid enzymes and hormone synthesis is temporarily restored, either by activation or production of enzymic agents. Their results in types of hypothyroidism without a metabolic block in hormone synthesis indicate that "stosstherapy" may be effective only in those instances in which an enzymatic defect is present.

*Sporadic Goiter of the Newborn.* The apparent common denominator in goiter formation of the newborn is increased secretion of TSH by the fetal pituitary in response to low circulating levels of "free" thyroxine. Endemic goiter of the newborn in regions where there is a deficiency of iodine in water and foods has been well documented. However, factors other than iodine deficiency may play a role[148]. In sporadic

goiter of the newborn the decreased thyroxine levels may be secondary to one of several genetically determined enzymatic defects in thyroxine synthesis or to placental transfer of goitrogens which interfere with thyroxine synthesis.

There is no evidence to support the possibility that in maternal hypothyroidism the fetal thyroid develops hyperplasia in an attempt to supply the mother with thyroid hormone. In fact, experimental and clinical observations indicate that the fetal pituitary-thyroid system develops quite independently in the absence of maternal pituitary or thyroid function[22,84,109,118,120,138,141]. In experimental animals neither endogenous nor exogenous TSH cross the placental barrier. However, the possibility that some abnormal pituitary or thyroid stimulating agent crosses the placental barrier in neonatal thyrotoxicosis may be worthy of consideration. From the foregoing observations it is not unexpected that sporadic goiter of the newborn results from diverse maternal influences.

While the infant with goiter is usually euthyroid, hypothyroidism and hyperthyroidism are relatively uncommon[18,78,115]. However, documentation of the status of the maternal and newborn thyroid function has often been inadequate in the reported cases, and furthermore some of the clinical signs of hyperthyroidism may not be as reliable in the newborn since tachypnea, tachycardia, and tremor may result from compression of the trachea and neck vessels by an enlarged gland[18]. Further confusion arises in interpretation of measurements of PBI and $I_{131}$ thyroidal uptake in those infants whose mothers had been receiving large doses of iodides or thiouracil derivatives.

In the series of congenital goiter collected by Bongiovanni *et al.*[18] and Packard *et al.*[115], goiters had been observed in infants from normal mothers, those with hyperthyroidism with and without treatment, those with hypothyroidism, those who received iodides or thiouracil derivatives, and those who did not receive any known goitrogens. It is entirely possible that case reports of infants with goiters due to unrecognized enzymatic defects have been included in these series. Whereas goiters due to iodine deficiency of the mother are relatively uncommon due to the widespread usage of iodized salt, goiters in infants of mothers receiving large doses of iodide for treatment of asthma or suspected hyperthyroidism account for a significant number of the cases of sporadic goiter[18,66,115,121]. Iodides in large doses are known to be goitrogenic in some individuals[100,116,133,157]. Interference with organic binding of iodine has been shown in humans and laboratory animals[116,149,168].

The placental transmission and goitrogenic effect of thiouracil derivaties is well documented. The fact that fewer infants born of mothers receiving thiouracil drugs do not have goiters is best explained by the observation that thyroxine administered to the pregnant animal crosses the placenta and inhibits the goitrogenic effect of thiouracil[74,80,120,141]. When hyperthyroidism in pregnancy is partially or adequately controlled with thiouracil, a similar protective effect of placental transfer of thyroxine is expected to occur. When maternal hyperthyroidism is overtreated with these agents, with resulting reduced transfer of thyroxine to the fetus, the balance is in favor of inhibition of the fetal thyroid by the goitrogen, which in turn leads to increased production of fetal thyrotropin and thyroid hyperplasia. In such instances it has been suggested that withdrawal of the influence of thiouracil results in a transient state of neonatal hyperthyroidism[18].

There are other goitrogenic drugs

and naturally occurring goitrogens in some foodstuffs but their significance in sporadic goiters of the newborn is not clear[31,53].

*Neonatal Thyrotoxicosis.* Unequivocal cases of neonatal thyrotoxicosis are relatively rare. Javett *et al.*[78] in 1959 summarized the findings in 9 cases. In each instance the mother had thyrotoxicosis or had been treated for thyrotoxicosis. Three of the mothers received thiouracil and iodide during pregnancy. Four were untreated and one had become myxedematous following thyroidectomy and received only 60 mg. of thyroid daily during pregnancy. Bongiovanni *et al.*[18] in their review, which included some equivocal cases of hyperthyroidism, noted that a goiter was found only after treatment of the thyrotoxic mother with thiouracil or iodide in all the reported instances except one.

It appears that neonatal thyrotoxicosis is transient and self-limited with recovery in the first few days or weeks of life[18,78]. As in adult thyrotoxicosis the etiology of neonatal thyrotoxicosis remains an enigma. It is most likely that the disease is related to the mother having had thyrotoxicosis during or before pregnancy. Although there is a significant placental transfer of maternal thyroxine to the fetus at term[54], which is probably increased in hyperthyroidism[22], this would not explain the prominent features of goiter and exophthalmos in the reported cases. Albeit, Langford[82] has produced exophthalmos in the fish with triiodothyronine. Furthermore, it has been pointed out that the reported therapeutic efficacy of Lugol's iodine is evidence against maternal thyroxine as the sole cause of thyrotoxicosis, but supports the thesis of overproduction of thyroxine by the fetal thyroid[78]. Also, the thyrotoxic newborn of the mother with myxedema would have received reduced amounts of maternal thyroxine[81]. The few reported pre-treatment measurements of PBI and $I_{131}$ uptake also indicate hyperactivity of fetal thyroid.

Thyrotoxicosis in the neonate of the mother who is "over treated" with thiouracil may be due in part to a rebound hyperactivity of the infant thyroid following the withdrawal of the goitrogen, but it does not explain those cases from the untreated or inadequately treated or postthyroidectomized-myxedematous mothers. In experimental animals "normal" endogenous and exogenous TSH does not cross the placental barrier and persumably the human placenta is similarly impermeable[119].

However, there are recent reports of an "abnormal" TSH in the serum of some thyrotoxic patients which elicits an unusually prolonged response of the release of $I_{131}$ from the thyroid of thyroxine treated guinea pigs[2,35,95,96]. So far this abnormal TSH has been found only in the sera from thyrotoxic patients. Adams[2] and Der Kinderen *et al.*[35] have suggested this is the exophthalmos-producing factor due to its presence primarily in cases of thyrotoxicosis with exophthalmos. It is possible that the human placenta is permeable to this "abnormal" TSH which in turn would stimulate the fetal thyroid and perhaps produce exophthalmos. A fetal pituitary stimulating agent from the mother traversing the placenta could likewise be postulated. One then must assume that the fetal pituitary is also capable of making an exophthalmos-producing substance.

**Summary and Conclusions.** In pregnancy, the most consistent alteration of thyroid hormone metabolism is an increased PBI and BEI concentration without signs of hyperthyroidism. An increased thyroxine-binding capacity of serum proteins secondary to the increased estrogen levels of pregnancy

explains this paradox. Placental transfer of free thyroxine depends on the relative binding capacities of maternal and fetal serum. The initial low TBP capacity of the fetus increases to above normal levels at term but does not reach the high maternal levels. Concomitantly, there is an increased transfer of maternal thyroxine. The placenta does not contribute directly to maternal or fetal serum concentration of thyroid hormones.

Development of fetal pituitary-thyroid system occurs independently of maternal pituitary or thyroid function. Biosynthesis of thyroid hormones in the fetal gland begins with concentration of iodide by the 14th week and proceeds to production of thyroxine by the 19th week in a pattern that parallels the sequence observed in the adult gland.

Early differentiation and development of the fetus apparently proceeds normally in the absence of thyroid hormone synthesis by the fetal gland and during a very slow placental transfer of maternal thyroxine. However, clinical observations indicate that in the latter half of fetal life thyroxine is essential for normal osseous and central nervous system development. Furthermore, the rate-limiting factors controlling placental transfer of maternal thyroxine do not adequately compensate for the absence of fetal thyroid hormone.

Serum PBI and BEI concentrations in the newborn are comparable to those of the mother at birth but increase further during the first 4 days of life. An increased avidity of fetal thyroid for $I_{131}$ apparently persists only until the peak circulating hormone level is reached. Increased erythrocyte uptake of radiotriiodothyronine also occurs during the newborn period, indicating that the high levels of thyroid hormone are not solely secondary to increased TBG capacity as in pregnancy.

Possible explanations for these alterations and for the absence of signs of hyperthyroidism in the neonate have been suggested. Hepatic immaturity of the glucuronide-conjugating mechanism and competition with other metabolites result in decreased biliary excretion of thyroxine with retention and saturation of available TBP. A decreased peripheral utilization, independent of the rate-limiting effect of TBP, is suggested by the high tolerance of new born infants for exogenous thyroxine.

Congenital disorders of thyroid function result from a number of genetic and acquired factors. An unexplained embryonic defect still appears to account for the majority of congenital non-goitrous cretins with aplasia, hypoplasia, or ectopic location of thyroid gland. Hereditary factors are relatively insignificant when compared to those in goitrous cretins with enzymatic defects.

Newer concepts of the etiology of non-goitrous cretinism favor destruction of the fetal thyroid rather than agenesis. An increased incidence of phenothiocarbamide non-tasters in non-goitrous cretins, their parents and siblings has suggested the possibility that the inherited inability to taste PTC may be associated with an increased sensitivity of the fetal thyroid to the biological effects of thiocarbamide goitrogens ingested by the mother. Placental transfer of a thyroid cytotoxic factor from mothers with autoimmune thyroid disease to their cretinous offspring has been demonstrated and implicated as a cause for some cases of non-goitrous cretinism.

The various inherited metabolic defects in thyroid hormone synthesis may produce congenital cretinism with or without goiter, or in less severely affected individuals, goiter without hypo-

thyroidism. Of considerable interest is the possibility that hormone synthesis may be temporarily restored in these enzymatic defects by use of short term administration of massive doses of active thyroid substances.

The apparent common denominator in congenital goiter formation is increased secretion of TSH by the fetal pituitary, secondary to low circulating levels of thyroxine. Goitrogens administered during pregnancy, primarily iodides and thiouracil derivatives, cross the placenta and interfere with fetal thyroid hormone synthesis. This mechanism has been implicated in the majority of congenital goiters not induced by enzymatic defects or endemic iodine deficiency.

Hypothyroidism and hyperthyroidism are uncommonly associated with sporadic goiter. Neonatal thyrotoxicosis is transient and self-limited, and seems related to the mother having had thyrotoxicosis during or before pregnancy. Rebound hyperactivity of the infant thyroid following the withdrawal of a goitrogen may occur in some instances of "over-treated" mothers but does not explain those cases from untreated, inadequately treated or post-thyroidectomized myxedematous mothers. Placental transfer of maternal thyroxine could not account for the presence of goiter and exophthalmos. Although "normal" endogenous TSH does not cross the placental barrier, it is possible that the placenta is permeable to the "abnormal" TSH recently identified in serum of some thyrotoxic patients. This, in turn, could stimulate the fetal thyroid excessively and perhaps produce exophthalmos.

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## OBSTETRICS AND GYNECOLOGY

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# MEDICAL HYPNOSIS AND ITS USE IN OBSTETRICS

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MEDICAL hypnosis, as a formalized therapeutic technique, has probably had more use in obstetrics than in any other field of medicine, save possibly psychiatry. A review of the experience gained by both obstetricians and psychiatrists, as they collaborated to develop obstetrical hypnotherapy and then continued their experiments with its practical use, should be of value to both obstetrician and the non-obstetrical physician. It is the purpose of this paper to review this experience which, in most part, has been gained during the last 30 years.

The sophistication of the medical profession varies widely in respect to the knowledge and understanding of medical hypnosis possessed by its individual members. This has led us to alter the usual format used for the review article. In consideration of it, we have added a special section, a "Preface" which follows these introductory paragraphs. The Preface consists of a sketch of the general subject of medical hypnosis, and its purpose is to provide background for those readers who might need some basic information on the subject. The reader who is experienced in the use of hypnosis may prefer to skip this section. This will not detract from his understanding of the rest of the paper.

The main part of the paper is devoted to the consideration of the three psychophysiologic methodologies most extensively in use for the preparation of pregnant women for childbirth and the subsequent conduct of their labors and deliveries. The first of these techniques might be termed the "purely hypnotic" or "hypnosuggestive" method. The others are the "Allied Techniques" of the title; first, "Natural Childbirth," the inspiration of Grantly

Dick Read, and second, "Psychoprophylactic Preparation," the corresponding methodology of Russian origin. Each method is presented separately. Next, the relatively few articles written about other uses of hypnosis in obstetrics are summarized. Finally, a commentary by the authors is appended.

The source of most of the material used in the body of the paper is the literature for the last 30 years. We read most of the pertinent articles in English during those years. These are included in the bibliography. Some papers that were reduplications of others were not included. Unfortunately, however, most of the important foreign writing, particularly, that in Russian and German, was not available. Those papers that were available have been included in our bibliography. Fortunately, we were able to complete our review because of an excellent book by Chertok of Paris. Entitled, "Psychosomatic Methods in Painless Childbirth" and published in 1959, it is an unusually complete review of the literature. Its value is enhanced by commentaries by the author. It has been capably translated into English by Leigh[15]. We have borrowed freely from this mine of information and particularly from that part of it dealing with the earlier Russian and German work. We have not plagiarized Chertok's bibliography, however, and we recommend his 587 references. We acknowledge our indebtedness to Chertok and his 260-page work, which every student of the subject should be familiar with.

We wish to acknowledge a second important source of general information. It is the tremendous wealth of unpublished experience that is the heritage of the modern student of hypnosis. The sources of this information have been personal conversations and communications, unpublished lectures, and a collection of material that was presented in seminars, symposia, workshops, and other training courses devoted to medical hypnosis. It is impossible for us to credit these sources, many of which have been forgotten. Nonetheless, they have influenced our thinking and have no doubt provided some of our material.

**Preface.** A summary of the recent history of medical hypnosis, particularly as it concerns current developments in the United States, introduces our general review.

The stimulus that revitalized interest in medical hypnosis resulted from its impressive and efficient use in World War I as an important part of the successful psychotherapy of many battle casualties. A repetition of this stimulus came with World War II, and it was the second wave of interest that popularized hypnotherapy in this country and opened the way for its ultimate acceptance by American organized medicine. All the credit for these advances, however, is not due to wartime psychiatry. During the years between the wars, important basic research was being conducted in this country by workers, most of whom were psychiatrists. Their work and a growth of general interest in psychosomatic medicine were also factors that helped establish hypnosis in American medicine.

In 1955, a statement of policy was made that was extremely important in the growth of medical hypnosis, particularly in the English speaking world. It originated in the British Medical Association[11]. Three years earlier, that Association had appointed a subcommittee of members of both the medical profession and the laity to investigate hypnosis as it applied to medicine. This subcommittee returned a very favorable report which formed the basis for the policy formulated by the Association. Hypnosis was acknowl-

edged and accepted as an important and valuable tool of medicine. Furthermore, the development of educational facilities was recommended for the teaching of the subject at both graduate and undergraduate medical levels. Finally, the creation of new research projects was urged and the expansion of old ones was encouraged. The fact that the Church of England was represented on the subcommittee helped to establish the ethical and moral status of hypnosis. This status was importantly reinforced the following year, 1956[74]. Pope Pius XII prepared a statement in which he gave his approval to and urged the use of psychotherapeutic means to relieve the pain of childbirth.

Meanwhile, medical hypnosis was experiencing growing pains in this country. There was a great demand for instruction from physicians in all branches of medicine. Unfortunately, facilities for this training were not available. Then, as now, most physicians had received little or no such instruction in medical school. Into this vacuum came the professional hypnotist. He was trained in hypnosis and was a student of human nature, as well he had to be. Uncontrolled by organized medicine or by the law of the land, he worked and lived honorably by a code of ethics that he developed. The field was his by forfeit. He was later joined by physicians, individually and in groups, who offered education in hypnosis by what is now usually referred to as the "short course." The faculties of some of these courses included excellent, ethical, and dedicated physicians. They played an important role in the development of hypnosis in this country, and they still have a place in the overall teaching picture. Unfortunately, this place has not been clarified officially and dissension has arisen in some quarters. Moreover, conflicts in the past had led to schisms among the workers. While the overall picture is healthy, these problems still trouble medical hypnosis and the medical profession.

The American Medical Association followed the precedent established by the British Association and released a statement of policy on medical hypnosis in 1958[3]. It acknowledged the use and value of medical hypnosis, recommended the development of teaching programs by the medical schools, urged the continuation and expansion of research in the field, and warned of dangers inherent in the use of this "new tool," if used haphazardly by physicians inadequately trained and ignorant of basic limitations and contraindications[88]. The Association appointed a Committee on Hypnosis responsible directly to the Council on Mental Health[4], to study the problems that could be expected as medical hypnosis is integrated into the medical armamentarium. To date, the efforts of the committee have been concentrated on expansion of the fields of education and research.

It is remarkable that a phenomenon as old as hypnosis should only now be causing such a flurry of official activity. This is because the specialty of psychiatry, or better, of modern dynamic psychiatry, is still so young and a basic understanding of hypnosis was impossible before its birth. Now that some of this missing knowledge is being added, the mystic and supernatural aura that surrounded Mesmerism is being replaced by an understanding that has had to develop before acceptance and use became possible and practical. This review attempts to characterize hypnosis in the light of the concepts of modern psychiatry.

Hypnosis can be defined as an altered state of mind of a particular type. It is a temporary, and if need be, a self-limiting state that is much more

closely related to the waking than to the sleeping state. Its development and utilization are the result of a particularly intense interpersonal relationship that develops between the hypnotist and the subject. The hypnotic state, the trance, develops in the subject as the hypnotist channels her mental activities into a point of concentration as he presents ideas and suggestions to her in a manner that will develop within her a response, preferably, the one he wants. As the trance develops, the subject's thoughts "turn inward," away from her environment, save the hypnotist. Her actions tend to be reflections of her conceptional rather than her real or experiential life[29].

A variety of phenomena may develop or be demonstrated in the trance. Some of these result from the state *per se*, while others are responses to the subject's spontaneous psychic activity, and still others are responses to the hypnotist and his suggestions. In listing some phenomena, no effort has been made to sort them as to origin. Rapport is one of the most important characteristics of the trance state. The altered state of mind of the subject results in the development of a relationship with the hypnotist in which her awareness is concentrated in the hypnotist and the relationship of the hypnotist to her. Concomitantly, consciousness of the rest of her real environment fades away. The most striking characteristic of the trance state is the subject's hypersuggestibility. Another important phenomenon is the ability to produce or develop analgesia and anesthesia. Additional sensory changes that may be demonstrable are hyperalgesia, blindness, and deafness. Catalepsy of specific muscle groups is made possible. Alterations in consciousness and memory may occur, for example, amnesia, hypermnesia, age regression, and revivification. Automatic writing and positive and negative hallucinations are possible. An interesting phenomenon is that by which the patient carries out a suggestion made in the trance state, after the hypnotic session has been concluded (post-hypnotic suggestion). In addition to these phenomena that are of psychic interest, there are others that show primarily somatic changes. For example, the physiologic activity of various organ systems, such as the cardiovascular system, may be altered. It is not surprising, in view of the complexity and diversity of hypnotic phenomena, that there is no single theory that adequately explains hypnosis[111]. The most comprehensive and complex of the explanations that has been suggested is the so-called "Psychoanalytic Theory"[38]. It attempts to explain hypnosis according to the accepted concepts of modern dynamic psychiatry. In oversimplified form it views hypnosis as a state of regression to a more primitive type of thinking in which the relationship of the subject to the operator is greatly intensified. The Russians, on the other hand, base their theory on Pavlovian neurophysiology. They view hypnosis as a conditioned state in which there is a generalized inhibition of the cerebral cortex. In this inhibited cortex, focal areas of excitation are developed. The third theory is one of fundamental simplicity. It is called the "role playing" theory. It explains hypnosis as a response to the existence or development of extreme motivation. These are but a few of many theories. It is apparent that complete understanding of the psychodynamics of hypnosis awaits the results of much more research.

The first consideration in thinking of hypnosis as a medical tool is, who should use it. At present, the only answer is professional men only: namely, physicians and dentists. In addition, one must remember that hypnosis is

not only an interpersonal relationship and an intrapersonal relationship involving the patient, but also one involving the hypnotist. The effect of these complex relationships upon the physician cannot be overemphasized. The physician-hypnotist should, therefore, be of sound mind. He should be normally adjusted psychically.

The next consideration is the training the physician should have. An ideal teaching program would be one given by a medical school with a trained teaching staff, available teaching material, and the usual ancillary facilities. Didactic lectures should be given on both hypnosis and basic psychiatry[24]. Supervised training-practice sections would be preferred. An effort to learn the best teaching methods, the material that should be included in such a course, and the amount of training is the goal of the Committee on Medical Hypnosis of the American Medical Association. Its investigation is being aided by "pilot" courses now in operation.

Once trained, the physician should limit his use of hypnosis to those medical situations that his medical training have qualified him to care for on non-hypnotic levels. Conscious of indications and contraindications, he should use hypnosis as only one of his many tools and should integrate it into his general therapeutic program.

Given the particular situation, the patient has now been completely diagnosed physically and the decision has been made to employ hypnotherapy. As Conn[17] has pointed out, ". . . the dangers of hypnosis are those which accompany every psychotherapeutic relationship. Any one who hypnotizes a pre-psychotic patient or psychopath . . ." is asking for trouble. A psychiatric evaluation appropriate to the situation and the planned use of the hypnosis is a prerequisite to beginning. The situation is explained to the patient and her misconceptions and anxieties about her situation or her therapy eliminated as completely as possible. These steps are essential to gaining the best trance state possible.

The patient's hypnotizability is the next point to be established. Estimates of the hypnotizability of the general public vary from about 40% to 95%[16,97]. The figures are meaningless in the given case, and even the ability of the particular individual in a given relationship to enter a trance will vary from day to day. These generalizations can be made: Children are good subjects. Usually, the adult who is healthy, intelligent, has good ego strength, is confident, and can concentrate, makes the best subject. If, in addition, she is an extrovert, responsive, and is imaginative, the situation is even better. The one thing she needs most for accomplishment is motivation. The physician can often build this or strengthen it. In developing the hypnotic interpersonal relationship, the characteristics of the physician also influence hypnotizability. Personality, prestige, and attitude are helpful qualifications. Confidence, interest, enthusiasm, and others, will vary the hypnotizability. Experience and training are valuable, especially for the difficult case. Fortunately or unfortunately, the average subject can be hypnotized just about as well by one person as another. In the long run, the best way to evaluate hypnotizability is to try to hypnotize the patient. With this thought, we do not even use tests to predict hypnotizability. There are a number of these tests that make use of the correlation between the patient's suggestibility and hypnotizability as an index for prediction[112].

There are many techniques that are in use for the induction of the trance state[111,112,116]. They have, however, a

basic similarity. The hypnotist attempts to center the patient's interest with growing intensity on himself. At the same time, he separates her from the rest of her environment, that is, he gradually eliminates the flow of stimuli that ordinarily govern her. Meanwhile, he has some immediate goal or endpoint that he attempts to reach by appropriate suggestions. Often this endpoint is eye closure. The stage operator, with his prestige and buildup and having carefully chosen a promising subject, would accomplish these ends by practically demanding them of the person who in turn expected them. Purely authoritarian techniques of this sort have no place in the normal doctor-patient relationship.

Most induction techniques used in medicine begin with suggestions for relaxation. As one suggestion is accepted, a response to another, even more complicated one, becomes easier. Simple suggestions are used at first and after the response has been obtained, more complicated ones are introduced. The patient is being taught to respond. By structuring the suggestions from the patient's actions and experiences, a smooth, atraumatic, and personalized induction is developed. The suggestions or ideas seek responses that are either sensory (ideosensory) or motor (ideomotor), and originate in a rather automatic fashion and free of conscious effort. The suggestions, even when subtle and indirect, must be clear. Repetition with variation makes them more forceful and definite. In the usual relaxation technique, relaxation is gradually deepened and eye closure is obtained. The trance has been induced.

The hypnotist may stop at this point and may utilize the relaxation and hypersuggestibility that he has developed. On the other hand, he may want to deepen the trance. This can be done in a number of ways. He may simply repeat the induction technique or use other simple inductions. Then again, he may utilize trance phenomena to deepen the trance. Thus, the production of hallucinations, catalepsy, automatic writing, and others, lead to deeper trances. Each new learning of the patient permits a more comprehensive state. Erickson[25,27,28,29], especially, has devised a number of ingenious methods by which to deepen trances. The trance can be terminated easily by simple suggestions to awaken. An occasional subject will not want to give up her trance but this need cause no worry. Special approaches can care for such a development but even if they are not used, the trance will terminate spontaneously within a reasonable time. Suggestions for the feeling of well being of the patient, a posthypnotic suggestion re induction of the trance, and appropriate praise to further the interpersonal relationship are usually given just before awakening the patient and they are repeated immediately after termination of the trance as reinforcing, waking suggestions.

Trance induction and trance utilization are quite different processes. The utilization is more difficult and is the primary source of danger. Since utilizations are individual to the particular needs, time and space do not permit development of this subject. The goal is approached by suggestions, direct or indirect, through any method of communication that is possible. While doing this, the hypnotist keeps the patient as a whole individual in focus. His duties are to guard and protect her and to avoid the disruption of checks and balances that govern her particular needs, and still to make progress toward his goal and the attainment of her needs.

The trance state, like sleep, can be graded according to depth as light, medium, or deep. The best classification

comes from the judgment of experience. There are tables that grade trance depth by the phenomena produced. This is not as scientific as it would seem, because some phenomena that are usually encountered only in the deep state may be produced easily in a given light trance, or *vice versa*. From a practical point of view, one attempts to attain that depth of trance that is necessary to the accomplishments the therapist has in mind. There are two other trance states that are categorized separately. The first of these is the somnambulistic trance. This is a deep trance in which the subject seems to be awake. The other and deepest of all trance states is the plenary trance. This state approaches suspended animation and has been utilized principally in experimental work.

Since the response attained in a given patient depends upon the depth of the trance, a variable is immediately evident as a source of misinterpretation when trying to compare the data from one reporter with that of another, who is supposedly reporting an identical experiment. In individual cases, there are other unpredictable variables. A given phenomenon may be produced in a given set of circumstances at a different trance depth for one patient, but the same phenomenon in another patient may need an entirely different set of circumstances. The ability of the patient to maintain a given level of trance, rather than fluctuating from one level to another, adds another ponderable for the uninitiated in research or the interpretation of it. An excellent paper on the subject of basic research in hypnosis was delivered by Gorton[41] at a symposium on hypnosis in 1960 at Colgate University.

To conclude this preface, a special word should be added about dangers. We refer you to the earlier statement by Conn. Serious, overt complications from the use of hypnosis are rare. They are, however, real. The greatest danger arises from subclinical or mild disruptions in the psyche of the patient. The greatness of the danger depends upon the relative frequency with which this might occur. One sees in practice iatrogenic problems that have developed at a nonhypnotic level. The intensity of the hypnotic relationship would seem to potentiate the possibility of such problems from careless management of the patient in a trance. This is just another way of saying that hypnosis may make the poor practice of medicine worse. These complications should never occur in the patients of physicians who are aware of these possibilities, have an understanding of basic psychiatric principles, and confine their use of hypnosis within the limits of their general medical training.

At the moment, another danger that is evident to every physician, is that incident to legal problems that might arise from hypnosis. This should not be a worry for the physician who understands the problem. The few cases that we know about are related to alleged sexual improprieties. The only decision that we know of that favored the plaintiff was in a case that most experts concluded was an hallucinatory rather than actual violation. Careful evaluation of one's patients before hypnosis would clearly reduce such a possibility. It is a good rule, however, never to conduct hypnosis in the absence of a protective third party. There are few laws that have been tested on this subject because of the rarity of the cases. There seems to be no significant danger at the present time for the physician using hypnosis. Attempts are being made to strengthen the statute books, and this particular situation should improve for the physician rather than deteriorate.

PSYCHOSOMATIC METHODOLOGIES OF OBSTETRICS. Psychotherapy has long been the keystone of good obstetrical care. When one considers that, even without any outside influence by the medical profession, the great majority of pregnancies would terminate successfully and in relatively uncomplicated fashion for both mother and newborn, one realizes that the psychotherapy originating from the doctor-patient interpersonal relationship is the obstetrician's primary contribution to most obstetrical patients. This psychotherapy is often so subtle that it does not even seem to be therapy. It consists primarily of many types of reassurance. By them he is contributing to "Childbirth Without Fear" by relieving or preventing fears and anxieties. The physician's personality, his attitude, and indeed, his very presence, are among the most important factors contributing to his patients' health and welfare. His routine examinations, his explanations of routine symptoms, and his answers to pertinent questions about the unknowns of the future contribute greatly to his patient's confidence. One might even say that group psychotherapy was an inevitable part of our "method." It is carried on by the patient's contacts with both the past and present patients of her obstetrician. An intangible of value stems simply from the fact that the patient is participating in what amounts to the "method of childbirth," that is the established and accepted one in her community. An example of this was experienced by one of us (G.L.H., Jr.) in 1935, at his first delivery as a senior medical student on an outpatient obstetrical service. The patient was a gypsy, who, for the moment, was in Philadelphia, far from her Argentine home. The labor and delivery were very satisfactory to the patient because they were conducted according to the morals, manners, and customs of her home. Throughout labor and delivery she squatted in the corner of her room and hid all those parts of her body that are important to obstetrics beneath a colorful, ceremonial skirt that was protected from within by ten petticoats. Anesthesia and analgesia were contributed by the chants of 3 other gypsy women, who were also attired appropriately for the event. Adherence to custom was all that was required to complete a normal delivery and a satisfying experience.

From this philosophy, one might say that every community and doctor has a personalized "natural childbirth" method, a fact that may account for much of the cynicism and even antagonism to the Read method that was and still is in evidence in the profession. When someone else's natural method is transplanted into another community or practice, the "natural" takes on a semblance of the unnatural. Be that as it may, there must be common denominators in all of the psychophysiologic methodologies that achieve the common obstetrical goals for them, namely patients who are usually pleased with themselves, their parturition, and their baby, and who have been relieved of serious pain and exhaustion, and who are both mentally and physically well as they start their healthy babies out into the world. There cannot be too many different neuropsychiatric and physical pathways by which the identical endpoint is reached. One would expect that an analysis of the specific methodologies that have been recommended for preparation for delivery and have been established and validated by the experiences of many doctors responsible for the care of many patients, would show us basic features, common and essential to any psychophysiologic approach. One might also expect that such a comparison might

give a clue to the values of certain distinct features peculiar to a given method.

*The Hypnotic or Hypnosuggestive Techniques.* The hypnotic method is the oldest of the three methods that will be presented. Although scattered reports of hypnosis used for labor and delivery dot the early literature, there was no formulated or organized plan of hypnotherapy in obstetrics until the Germans introduced their "hypnosuggestive" method shortly after World War I. This work impressed the Russians, and soon after the early German reports appeared, the Russians were applying the method.

Friedlander[34], Falk[31], Heberer[45], Kirstein[50], Siemerling[95], and Liegener[64], were among the pioneers in Germany, and their work appears in the literature of the early 1920's. Schultz-Rohnhof[94] and Kogerer[53], were, however, the leaders in most of this German period. These men were obstetricians, and attention is called to this because of the contrasting situation in Russia. There, Platanov, a psychiatrist, and the director of the School of Psychotherapy in Kharkov, was responsible for the introduction of obstetrical hypnotherapy. He remained the leading figure in this field and was the one most influential in the creation of psychoprophylactic method, which was to follow in 1951. Platanov and his school were interested in the application of psychiatry to the problems of general medicine. He was soon joined in his obstetrical venture by Nicolaiev, an obstetrician, and by one of his own pupils, Velvoski. They proved worthy associates and, with Platanov, remained the "big three" of psychophysiologic obstetrics in Russia for years.

The German hypnotic method, with its Russian adaption, is essentially the method we are using more than 25 years later. Schultz-Rohnhof's technique included: antepartal correction of misconceptions and fears of hypnosis; antepartal preparation of patients and the introduction of group therapy; the use of posthypnotic suggestion given before labor to create a beneficial substrate for pain relief during labor; and the use of hypnosis during labor and delivery so as not to deprive the patient of an important, personal experience. The routine of Kogerer was practically identical. If anything, his method placed more emphasis on the use of posthypnotic suggestion for analgesia in labor. The primary difference between these men was their attitude toward the importance of the presence of the obstetrician during labor. Schultz-Rohnhof insisted that the obstetrician's presence was of the greatest importance. Kogerer said it was not, therefore the emphasis on the posthypnotic suggestion in his technique. It would be unjust to conclude that Kogerer's 70% of excellent results and Schultz-Rohnhof's 80%, measured the importance of the presence of the obstetrician. By a good result was meant that the patient was pain free without analgesia or anesthesia throughout labor and delivery.

The Russians were more interested in the reasons for the use of hypnosis and upon its effects on the mother as an individual, the mother-baby relationship, and the like, than were the Germans, or, at least, they wrote more. This is probably a reflection of the value of the rather unique collaboration of obstetrician and psychiatrist made possible through their growing experience because they continued to apply the method vigorously. The German literature on the subject practically disappears after the flurry of the first few years of publishing. Platanov saw hypnotherapy not only as a means to pain relief but as a part of a methodology that could avoid maternal ex-

haustion and protect the labor passenger from drug toxicity, and had many ancillary advantages. After more than ten years of experience with the method, he was still publicizing "additional values," for example, a beneficial effect on maternal attitude and the development of a particularly satisfying mother-baby relationship.

It is not surprising to find these "plus values" appearing in the American literature almost from its inception. This broader appreciation of the advantages of hypnotherapy in obstetrics was conditioned by the Read method, which preceded it, and by the general growth of psychosomatic medicine, which also preceded American activities in the field. Most of our publications on the subject have appeared in the last 5 years. Indeed, the use of hypnotherapy on a wide scale is almost confined to the same 5-year period. This does not mean there was no experience in hypnosis before that, for it was being used in obstetrics sporadically even before World War II[68]. Kroger and DeLee[54] published their first paper on the subject in 1943. Before the official statements of policy by British and American medicine, however, hypnotherapy was being used quietly and only by the occasional obstetrician. Most doctors did not want their names associated with hypnosis. Many hospitals, perhaps the great majority, would not permit its use within their walls. During this same period of time, there was no great demand for the use of hypnosis in obstetrics.

The declarations of the American and British Medical Associations[3,11] have dramatically changed the situation, although admittedly, acceptance by both the profession and the laity limit and probably will continue to limit the widespread use of obstetrical hypnotherapy[13]. At least, hospital doors are open now to the use of hypnosis; it is finding greater lay appeal; and the physician who practices it need no longer feel like an isolated pioneer.

It is likely that the main indication for hypnosis in American obstetrics is the request for it by the individual patient. Our estimate, admittedly a vague guess, is that most obstetricians who use hypnosis employ it for no more than 10 to 20% of their patients. There are notable exceptions to this and probably they are due to the reputation of the individual physician. In those who routinely suggest its use to their patients, one hears figures of acceptance that vary from 30 to 50%.

One of the benefits of hypnotherapy as a psychophysiologic approach to obstetrics is its great elasticity. The individual obstetrician can develop the method that suits him best and can individualize it, in addition, for his patient. The lack of standardization presents a problem, however, to one trying to make comparisons and "explain" policy. Both the Russian and German methodologies stressed with great emphasis the importance of the educational feature during the antepartum period[2,76]. They suggested 4 to 6 visits during the last 4 weeks of pregnancy. Two or 3 of these sessions were individual sessions and the rest were group sessions. The groups included, when numbers are given, about 25. At the individual sessions, misconceptions were clarified and the development of the hypnotic state was accomplished. The group sessions were primarily for the relief of anxiety and fear by education. This may have been a superficial reason for the group therapy. Both the Germans and Russians were extremely aware of the psychological values inherent in group therapy, *per se*. Their experience taught them that there was little point in increasing the number of sessions in order to attain a greater number of successes. Indeed, they em-

phasized that one could decide quite well from experience how a given patient would develop by observing her capabilities at the first session. In other words, if the patient immediately proved to be a good subject, she would continue to be one. If she was not, or, at least, was not in that particular environmental situation of which she was a part, she would not improve remarkably in her responsiveness. Since patients in this country apparently report much earlier and are seen more frequently by their obstetricians during the antepartum period, the educational aspects of the method are usually accomplished in small parcels distributed throughout pregnancy, rather than in the formal, concentrated method of the Russians. Although appreciating the value of group therapy, American obstetricians, in most part, have so few patients who are interested in hypnotherapy that it is difficult to form a sizable group. There is, therefore, less group work here than abroad, and that relatively informal. For the same reasons, the obstetrician rather than a nonprofessional associate usually directs each session. Contrasting with the practices of the majority, there are notable exceptions. Excellent obstetricians, who are long established in hypnotherapy by time and reputation, have large numbers of patients in training for hypnotic care. These men may teach both trance induction and the didactic material about pregnancy in group sessions. The patients may be introduced to the subject by pamphlets that explain the hypnotic phenomenon and dispel the usual misapprehensions. There is widespread use of records and tapes that are reviewed in the office and then taken home by the patient for practice sessions. Some obstetricians teach autohypnosis by relaxation exercises similar to those of Read. Thus, many combinations of antepartal techniques are used. Probably a large percentage of patients are trained individually and without the help of a group.

The main problem stemming from the use of these techniques has been the same both here and abroad. It is the extra time required for each patient. Indeed, this was an important reason for the introduction of psychoprophylaxis in Russia. A number of suggestions have been made to lessen this time. The Russians emphasized the use of posthypnotic suggestions for pain relief, given during the prenatal sessions for recall in labor. This technique has had increasing appeal in this country. A second step toward practicality has been in an attitude toward planning the conduct of labor by a combination method of hypnosis and drugs. Here the preplan is to use sedation and anesthesia but to strengthen their effects by hypnosis, thus greatly reducing amounts needed[29]. In such cases, little or no unusual preparation is required and the hypnosis is employed practically as an extemporaneous, adjunctive technique. This combination serves well. The Russians have used extemporaneous hypnosis frequently without preparation, adding sedation if and as needed. They emphasize the importance of motivation, in this case by pain, and rarely begin the induction before cervical dilatation of 8 cm.[3]. With this technique as well as their preplanned methods, they often use the suggestion inherent in placebo therapy[2]. Another timesaver to the obstetrician during his conduct of labor that has been emphasized by Kogerer[53] and others stems from the relative ease with which hypnotic rapport can be transferred. Thus, the obstetrician can transfer his ability to care for the parturient to any attendant while he is elsewhere. This possibility of the successful transfer can be in-

creased by appropriate antepartal posthypnotic suggestion. The physical presence of the obstetrician, however, is still a *sine qua non* for success in the minds of many. Jacobson[48] insists that this is a primary weakness in obstetrical hypnotherapy. He points out that it weakens the patient's ego strength by fostering dependence.

The methods of hypnosis that are used during labor are about as variable as those governing the antepartum techniques. Although little detail about this appears in the foreign literature, it seems likely that the trance is usually induced by routine relaxation or authoritarian techniques, taught antepartum and reinforced by posthypnotic suggestion. This remains true in America. Utilization or naturalistic techniques[29] are being employed more frequently as evidence of the influence of Erickson's extensive teaching. He has also pioneered in teaching the more advanced special techniques, for example, "dissociation" and "confusion" techniques, that should result in deeper and more stable trances, and thus lead to better end results. He has also demonstrated the value for the parturient of developing "time distortion," the ability of the hypnotist to alter the apparent length of time[26]. By the utilization of this trance phenomenon, the length of contractions can be made to seem shorter than they are, the resting intervals, longer, and the overall time of labor, shorter for the patient.

Reports of results of the use of hypnosis concentrate attention on relief of pain. These are difficult to evaluate because all that they really show is what one man can do with his particular practice, which, although unselected by him, is really very selected as a result of his reputation. One would think that the foreign groups, particularly the Russians, are more truly unselected. An "excellent" result is usually defined as a patient who requires no sedation nor anesthesia for labor and delivery. A "good" result is the case requiring minimal drug therapy or anesthesia, or both. The Continental literature reports excellent results in 50 to 90% of hypnotized patients. Uniformly, both here and abroad, failures are in the range of 10%. Results in this country based on complete or relatively complete freedom from pain range from 35 to 90%[16,52,56,70,91] with a median a bit less than 50%. The great variation in the data is probably the result of selection. One should emphasize, too, that the results indicate a success rate in patients using the technique, not of those in the author's whole practice. Some investigators try to use the method in almost all cases, others, in relatively few. It is often stated that a trance deep enough to insure excellent results is at most 25% of a cross section. Relief of pain is admittedly the primary goal of most authors using them. Relief of anxiety is coupled automatically with it[1,21,35,42,43,60,72,75,108,113]. One can say almost with certainty that drug requirements for pain relief will be lessened for every hypnotized patient[16,35,55,72]. A corollary of this postulate is that one can anticipate newborns from mothers hypnotized for labor that are less narcotized and less asphyxiated than those from more heavily sedated patients, and this is almost a universal impression of those reporting. Other advantages are reported from hypnotically conducted labors. Reynolds[84] called attention to the impressive relaxation of somatic musculature. Apparently the result of this, a decreased incidence of paravaginal and perineal lacerations has been reported[20,65,115]. As experience with hypnoanesthesia increases, more and more major surgical procedures are being done under hypnosis[47]. A number of Cesarean sections have been accomplished success-

fully under hypnoanesthesia in this country[58,60,71,85,115] and abroad. Crasilneck[18] has pointed out the particular value of hypnoanesthesia in complicated cases. It seems to us that the satisfactory evaluation of a psychosomatic technique by percentages of pain relief is very unreal. Admittedly, however, endpoints on which to base statistical reports are a well-known problem in hypnotic evaluation. A true evaluation, however, should take account of the many other effects that accrue from the hypnotic relationship. If the operation cannot be accomplished under hypnoanesthesia alone, pre-anesthetic hypnosis greatly reduces the amount of anesthesia that would have been required and, at the same time, reduces the probability of shock and postoperative complications. Hypnotic labors are shorter than average, the decrease averaging about 2 hours[13,26,60,70,114]. Most observers comment that postpartum blood loss is reduced[21,59], possibly through vasoconstriction[57]. Winkelstein and Levenson[115], however, found no change in blood loss. Almost all who use hypnosis in labor are greatly impressed by the good attitude it engenders in the new mother and the apparent conservation of strength it has accomplished[8,10,12,21,22,35,54,60,77,113]. There is no question that a majority of these patients do not share in postpartum exhaustion, are relaxed, and feel surprisingly well after delivery. The maternal pride and satisfaction in her accomplishment are excellent.

The extra time required by the obstetrician using hypnotherapy remains its greatest drawback. In addition, the old mysticism associated with hypnosis remains, and for many it remains unacceptable[13]. An apparently insurmountable disadvantage lies in the number of patients who cannot be hypnotized or for whom a sufficiently deep trance cannot be accomplished. Stewart[96,97] found that only 20% of his patients could obtain a deep trance state. On the other hand, he only had complete failure in 10%. Winkelstein[114] estimated that he could not help 30% of his patients by hypnotherapy. Weighing advantages against disadvantages, those who use and write about obstetrical hypnotherapy are impressed by its value. Tom[99] and others caution about overenthusiasm until greater experience will permit a better evaluation of the problem.

*"Natural Childbirth:" Grantly Dick Read.* A book by Grantly Dick Read, "Natural Childbirth"[79], was published in London in 1933, and it was destined to have a tremendous impact on psychosomatic obstetrics. The book was the outgrowth of an experience that had left an indelible impression on Read. He delivered a patient, who had had an amazingly easy labor without help of any drug or anesthetic. When he questioned her about it, she answered, "It was not meant to be painful, was it?" This incident influenced the rest of Read's life. He decided that normal labor, a physiologic process, could not be painful. None the less, women had pain with childbirth, and he devised a theory to explain this. The theory was completely empiric and its development was based on unproved and unprovable assumptions. His book presented his theory and his solution for painless childbirth.

The tenuous basis for his theory almost led to its early destruction. The book had appeal, however, particularly for the laity. It was a success. This support was all that Read needed. With almost religious zeal and missionary spirit, he publicized his method and his faith in it. His sincerity, honesty, vigor, and driving personality spread the gospel throughout the world and won for him many disciples, even more

zealous, if this were possible, than himself.

Read's theory had the appeal of simplicity. A normal event like childbirth could not be painful. His denial of original pain from labor and delivery was fundamental to his method. The fear and anxiety led to tension and, in turn, to pain. Read admitted that other factors in the patient's background did influence the situation in some degree. Among these influences were the patient's personality, her general health, and her state of mind, which was at the mercy of fatigue or every day stresses and strains, or both. His pseudoscientific explanation of primary pain was, therefore, the cortical misrepresentation of the visceral stimuli from the contracting uterus. The theory proceeded then to assume that this misinterpretation plus anxiety activated the cortex in abnormal fashion. In turn, it discharged abnormal nerve impulses down over the autonomic pathways, back to the uterus. These abnormal stimuli produced abnormal uterine contractions. These abnormal contractions did produce painful stimuli and, arriving at the cortex, were exaggerated by its already excited state. Thus, the problem of pain was produced from the sum of a primary and a secondary pain.

Read's solution to the problem was as elementary as his theory. One must simply eliminate fear and anxiety and pain would be prevented or controlled. To eliminate them, he developed a three-point program. The first part of it was educational; the second, physiotherapeutic; and the last, psychotherapeutic.

The educational part of his program was presented to patients in groups, and occupied the last half of pregnancy. An elementary lecture course and demonstration about the anatomy and physiology of pregnancy, involved in the growth of labor and delivery was the essential element of teaching. The physician presented a number of these sessions, and a well trained nurse or midwife gave the others. The second part of the method, the physiotherapeutic part, consisted of three kinds of exercise. These were also taught in group fashion. The first set of exercises involved controlled breathing, designed basically to foster relaxation throughout labor. The exercises were different for different stages of labor. The second type of exercise was the relaxation exercise. This consisted of tensing and then relaxing individual muscle groups throughout the body. Read credited Jacobson[48] as the father of this method. Jacobson was never complimented by this accreditation because he did not think much of Read's relaxation technique. Admittedly, the two methods have something in common but the Jacobson method is a much more thorough and complicated system than Read's, and, as a result, produced a deeper and better controlled state of relaxation. The third group of exercises was designed to improve the patient's general health in nonspecific fashion. Interestingly enough, these exercises are those that have characterized the Read method. They are the least important part of the method.

The psychotherapeutic part of Read's method had so many facets that, in their subtlety, many were never noticed by many physicians. Both of the first two parts of the method were extremely valuable psychotherapeutically. Probably the most important features of the psychotherapy were, however, Read himself and the symbol he became. He demanded, or at least, got, undivided loyalty for his method from all those who worked with him in the care of his patients. "His" group engendered an atmosphere of undeniable importance that surrounded his patients from

mid-pregnancy to the end of labor. He knew the importance of this and tried to improve it in every possible way. He did his best to eliminate all "negative stimuli."

Group training was an important part of the psychotherapy. The psychodynamics of group work are too complex to discuss in this paper, but its advantages are many. His relaxation exercises would produce a trance state in many patients. He utilized the hypersuggestible quality that came with relaxation. His books on the subject, as well as those by others[36,40], his personal visits and his other contributions to the literature added prestige, which was of no little importance.

Niceties were added to the method as the result of experience. Because many of the labors were not painless as most people were led to believe they would be, Read changed the title of his second edition to "Childbirth Without Fear"[80]. Efforts were made to permit the use of minor amounts of analgesia and anesthesia during labor and delivery without "loss of face." The husband was encouraged to be with the patient[33,63,105], and he was taught to carry out certain procedures designed to support the patient in labor.

In America, interest in Read's method dates to the immediate postwar years. Sawyer[90] was one of the pioneers of the Read method in this country. He published his first paper about it in 1946. The following year, Read came to America by invitation of the Maternity Center of New York, and another wave of interest was engendered. Goodrich[40] at Yale was an important convert to the method. Thoms, who followed Goodrich, contributed still more through his interest, lectures, and numerous publications[101,102,103,104,106,107]. His important contributions were rooming-in and prenatal pediatric consultations. He expanded the use of sedation in reasonable amounts. Well oriented in psychodynamics, Thoms emphasized the importance of the method for its contribution to certain emotional needs of the mother and to the mother-child relationship. It is interesting that he vigorously denied that "Natural Childbirth" was related to hypnosis. Buxton[12] followed Thoms. He has also emphasized the method as of value to accomplish an emotional experience. Winkelstein and Levenson[115] also emphasized the experiential value, and Davidson[19] pointed out that the essential feature of the method was the satisfaction of participation. Many other publications appeared about the Read method, stressing one or another of its aspects or offering some refinement of another value[19,61,71,73,77,87,93,110]. Results of the method were relatively uniform[71,82,96,104,109,110]. Twenty-five to 30% of the patients had no pain. Fifty per cent had good results. Complete failures were less than 10%. Additional values reported by some and denied by others included the shortening of labor, the development of personal satisfaction, and freedom of the baby from depressing effects of analgesics and anesthetic agents.

The publicity given the Read method and the misunderstandings of it led to many discussions and even arguments. The question as to whether it was or was not hypnotic, Read, Goodrich, Thoms, and many others answered in the negative. Kroger, Mandy[67], and many Americans[5,8,9,37,39,78] insisted it was. It was said to be "too superficial"[67], it produced dependency[18], it was dangerous[86]. It seemed that a technique of this sort might appeal to the needs of the prepsychotic, and this was no doubt why Rogers[86] was able to find 9 cases of psychoses associated with it. That the method was at fundamental fault would be an unwarranted conclusion. Despite controversies, it produced many satisfied mothers.

*Psychoprophylactic Preparation.* In

1951, the Russians presented their new method of psychophysiologic obstetrical care. It was described in a bulletin from the Ministry of Health entitled, "Temporary Directions in the Practice of the Psychoprophylaxis of the Pains of Childbirth." The two leaders of the committee that formulated the plan were the two pioneers of obstetrical hypnosis, Platanov and Velvosky. It grew out of the hypnosuggestive method, but did not replace it completely. The original method was preserved and assigned for use in difficult or complicated cases.

Psychoprophylaxis replaced formal hypnosis for two reasons. First, a Russian law had restricted the use of hypnotherapy to certain qualified physicians. Second, the hypnosuggestive method required more of the obstetricians' time than they were able to give. The hypnosuggestive method became impractical of general application, and was replaced for expediency, not for inadequacy. Basic construction of the psychoprophylactic method is remarkably similar to that of Read. There were three important obvious differences between the methods and a number of secondary differences. The differences are advantages in the opinion of the Russians. First, the method had a defendable scientific basis in Pavlovian neurophysiology. Second, it was presented in a carefully detailed fashion, well organized, and unmistakably clear. Finally, status for it was guaranteed from the start because it was a declaration of the government.

In the new method, instruction of the patient was of prime importance. Whenever possible, four to six sessions of training were scheduled for every patient, beginning at the 36th week. A modified shorter course was available for special emergencies. Four sessions or more were required for statistical reporting. As a second important feature, the active participation and personal physical presence of the obstetrician were emphasized. He was personally to begin the patient's training by conducting the first session. He was obligated similarly for the last. Interval sessions could be turned over to mid-wives. Furthermore, he was expected to be with the patient during labor. At the original session, a complete medical evaluation was required. An equally careful psychiatric evaluation came next and all data were recorded and the patient classified for the antepartum record.

The educational program was designed to develop in the patient a positive emotional attitude toward her pregnancy and childbearing. To accomplish this, good teachers with suitable personality traits were a necessity. Even the required characteristics and attitudes of this personnel were detailed in writing. The established educational precepts of the hypnosuggestive method were taken over intact. Special attention was given to the correction of misconceptions and the elimination of fears and anxieties. Appropriate physiology and anatomy were taught. An extra refinement was the grading of patients according to intellectual and cultural backgrounds. Patients with similar backgrounds were united in separate classes so that the teaching could be carried out at the intellectual level of the patient.

The Russian method accepted as fact that normal labor is painless, and in this assumption they followed Read. A painless labor could be anticipated, therefore, if the patient learned her lessons well. This challenge was kept clearly before the patient. The teachers were urged to be enthusiastic, communicative, kind, and understanding in their work. Expansion of motivation was a teaching duty. To further this, the patient was introduced to a woman

or women who had successfully employed the method. The staff was taught the importance of suggestion at all levels and they were expected to incorporate it into their teaching methods and use it actively.

"Pain reducing procedures" carried out by the patient were the substitution for Read's exercises. Controlled breathing, with attention to the rhythm of breathing, was retained. The first "pain reducing procedure" was circular effleurage of the lower abdomen in time to the breathing. When these could no longer control discomfort, the next procedure was introduced to replace the effleurage. The second procedure was to make pressure with the thumbs on the anterior, superior iliac spines during contractions. When necessary, the next procedure was put into practice. This consisted of making pressure against the lower back with the dorsal surface of the hands. The specific pressure area was that bordered by the rhomboid muscles. Finally, instruction was given in sphincter relaxation.

The next important element in the method was a relaxation component. This differed radically from Read and hypnosuggestion. The relaxation was developed actively rather than passively. This "activity" or purposefulness was essential in theory because, to transform the method from a hypnotic to a nonhypnotic one, an active cortex was required by Pavlovian theory. The active relaxation and the "procedures" accomplished this.

The authors of the method were willing to admit that in carrying out the method an "hypnoidal state" was developed. They agreed, too, that the patient was hypersuggestible in this state. Re-emphasis was placed on utilization of the hypersuggestibility, both directly and indirectly.

The presence of the physician during labor and delivery remained of paramount importance. He was required to be present at least at or near the time of admission, at the time of any personnel change, and, of course, for delivery. Great importance was placed on the times at which the various "procedures" were introduced in labor and this decision was the responsibility of the attendant. Suggestion was used liberally. Detailed attention was directed toward a good environment for the parturient; for example, all restless patients were isolated.

In 1956, a conference was held in Kiev to re-evaluate the psychoprophylactic method. At this meeting, the official title of the method was changed. It became "The Psychoprophylactic Preparation of Expectant Mothers for Childbirth." Thus, painless labor which was promised in the original title, was no longer promised. This change was needed because childbirth was often not free of pain, and having been promised this, some patients were destroying the propaganda surrounding the method by their complaints. The conference also suggested more liberal use of supplementary medication and re-emphasized the importance of suggestions, and particularly those of an indirect and subtle type.

Collection of comparable data for statistical study was insured as best it could be by clear and definite rules on the subject. Excellent or good results were obtained in 75 to 90% of cases. Completely painless labors, however, averaged only 40%.

Attempts were made to check these results as objectively as possible. The changes in blood adrenalin levels were correlated with reports of subjective pain. Similar work with acetylcholine levels was done. Electroencephalographic data were included. These tests and others seemed to confirm the purely clinical results which had been re-

ported. Although good results were obtained in 80 or 90% of cases, half of these successes were made possible by discipline rather than complete pain relief.

The method appeared, therefore, to produce the required reduction or elimination of pain very satisfactorily. Fears and anxieties were eliminated. In addition, labors were shortened and there was a decreased incidence in operative delivery and the use of episiotomy when data were compared with those controls. Eclampsia, uterine inertia, and pelvic lacerations were reduced. The general health of the newborns was improved in the study group and fewer evidences of fetal distress occurred during labor. Finally, the patients using the method were impressively better as to strength and mood than was true for the others, and this was reflected in the greater weight gains reported for their babies.

To date, there has been little demand and little use of the Russian method in the English-speaking countries. Its popularity has been growing, however, on the European continent, particularly in France, and in South America and the Orient. Lamaze has championed the method in France. The French have modified it in one important way. They prefer passive to active relaxation but insist the "procedures" keep the cortical excitation that is essential. A minor change in breathing exercises is the only other French change. The French results are similar to those reported from Russia.

*Miscellaneous.* Several statements have already been made in the presentation as to the apparent advantage that a hypnotically conducted labor has for the newborn. Evidence of the correctness of this impression has been offered in two recent studies. Moya and James[73] studied newborn infants from mothers whose labors and deliveries had been conducted under hypnosis and others from parturients given no analgesia and no more than local anesthesia. Both groups of babies were very mildly asphyxiated as determined by acid-base studies of infant blood. Continuing serial acid-base determinations showed, however, that the values became stabilized and reached normal levels significantly more rapidly when hypnosis had been used.

Escardo and Coriat[30] studied the tonic antigravity conduct of newborn infants in order to evaluate "birth shock." "Birth shock" was absent or almost absent in all newborns delivered from mothers using psychoprophylaxis. It was present and did not disappear until at least the fourth postpartum day for most newborns delivered by "customary methods." As Flowers[32] has pointed out, however, neurologic morbidity and alterations in the reactivity of newborns are more often traceable to birth trauma than to analgesics or anesthetics given the mother. Escardo and Coriat admittedly do not know the significance of their finding, but, as they point out, it seems likely that reduction in "birth shock" should be one additional sign indicating a better prognosis for the infant.

Other laboratory data that relate to clinical observations have been referred to in the studies by Reynolds[85] on the effect of hypnosis on uterine contractility. He demonstrated that contraction patterns could be altered by hypnosis. Baer[9] confirmed these observations by tocographic studies. We have reached these conclusions from works of our own done with the Lorand tocograph. The changes that result spontaneously from induction of the trance state are toward the normal or ideal, that is, toward the most efficient type of contraction.

A number of papers on other uses for hypnosis in obstetrics are worthy

of mention. August[7] and Clark[16] have used hypnosis to improve and to inhibit lactation with satisfactory results.

Several investigators have reported experience with hypnosis for the treatment of hyperemesis gravidarum[7,37,39,52,57,91]. The success rates varied from 50 to 100%. Hypnoanalytic methods have occasionally been resorted to with success in the treatment of refractory cases.

Ptyalism is, we realize, not infrequently treated successfully by hypnotherapy. We encountered no mention of this use in our survey, but it is likely that we missed it. We have successfully treated all of the 3 cases we have encountered. Results were prompt. The method employed was a combination of relaxation, relief of anxieties, and direct suggestion.

COMMENT. A comparison of the bases of all three psychophysiologic obstetric techniques shows clearly their common structure. Although the theories by which to explain results vary widely, other dissimilarities are primarily a matter of emphasis and detail.

The immediate goals of each method are the prevention and relief of pain through physiologic processes. Accomplishment of these aims provides an opportunity for the patient to participate consciously, cooperatively, and satisfyingly in her labor and delivery and negates a need for excessive sedation and anesthesia.

Basic to these attainments are the state of mind of the patient and the utilization of that state by the obstetrician. Occasionally, the necessary state of mind is a natural attribute of the patient. This was apparently true in Read's original case. More often, it must be developed, and the development is the responsibility of the obstetrician who chooses to use this type of obstetrical preparation. Here, then is most of the fundamental background of hypnosis: an (altered) state of mind developed by an (intense) interpersonal relationship and influenced and utilized by the (hypnotic) operator.

At the onset, the practitioner of each method develops or strengthens motivation in his patient by every possible means and he continues to reinforce it. An educational program is an important constituent of all three techniques. In the overt hypnotic method, much of the learning is directed toward the correction of unwarranted fears and misconceptions about hypnosis. In the "Allied Methods," the advantages of the method are stressed. Common to the educational programs of all three is the presentation of fundamental information about pregnancy, labor, and delivery. The purpose of this part of the methods is to relieve the mind of the common fears that relate to childbearing and the anxieties of the unknown that face almost every pregnant patient. This mental conditioning is essential to the development of the receptive state of mind. Since trance induction in itself produces this alteration in mental status, the hypnotic technique requires the least obstetrical didactic training.

The physical therapeutic portion of the three techniques vary considerably as one compares one method with the other. The dissimilarity is, however, superficial. One can dismiss the physical exercises of Read as of little significance, although they have received a great deal of attention. They are, according to Read, only a part of the general health campaign that is the essence of the physical fraction of all antepartum care. They do, however, have some psychologic value as indirect suggestions. One can view the other "exercises" and "procedures" of the "Allied Methods" as trance induction devices. In the Read Method, the im-

portant relaxation exercises are comparable to the suggestions for relaxation and sleep given by the hypnotist. The breathing exercises are diversionary and focus the patient's attention "within," and at the same time, compound suggestion by joining the breathing to relaxation, and later, to expulsive efforts. Thus, they accomplish the same purposes as eyefixation and the compounding suggestions of the hypnotists. The "active procedures" of the Russians are similar to the active "utilization techniques" of Erickson. The Russians, however, unlike Erickson, structure the activities that are to be utilized for direction of attention and the gradual exclusion of the surrounding, physical environment.

One concludes that all three methods develop a trance state. In the "Allied Methods" it is deepened by repetition of the exercises and procedures. In the hypnosuggestive method, even greater trance depth and stabilization are possible through the multiplicity and variety of deepening procedures.

Once a trance is induced, utilization is governed primarily by the phenomenon of hypersuggestibility. The "Allied Methods" stress and restress the importance of direct and indirect suggestion. Less emphasis is placed on this in the formal presentation of the hypnosuggestive method because all physicians trained in hypnosis are already acutely aware of the importance of suggestion.

Additional comparisons can be offered to show similarities shared by the three methods, but sufficient evidence has already been offered to justify the conclusion that all three are basically hypnotic techniques. This is an important conclusion, not for the sake of settling an argument, but rather, for the essential knowledge that it gives the physician who employs one of the "Allied Methods." The additional understanding, engendered by this realization is essential if the techniques are to be utilized to their greatest advantage. Indications and contraindications, values and dangers, and strengths and weaknesses of the methods become more clearly apparent. A physiologic means of controlling pain becomes available, and this too is important. A basic assumption of both Read and the Russians was that normal labor was painless. This assumption does not seem tenable. If organic pain is to be relieved, this can be done physiologically only by hypnosis. If one does not realize he is using hypnosis, complete pain relief by the method becomes a matter of chance.

It seems probable that many failures of the Read method in this country resulted from the misconception that pain is relieved automatically if the patient carries out a purely physical routine and is reassured. Even if a trance were accomplished, it would not produce complete anesthesia. Correct utilization of the trance, however, can relieve and even eliminate pain. Many successes obtained by the Read method were borne thousands of miles away. Read gave his suggestions to the patient and utilized the trance for the physician through his writings and reputation. The essential rapport was between the patient and Read, whom she never met. The local obstetrician was only a symbol of Read, and in successful cases, rapport was temporarily transferred from Read to the patient's doctor.

All three psychophysiologic methods have demonstrated their values in preparation for childbirth, delivery, and the postpartal period. A thorough understanding of hypnosis, its limitations, dangers, and complications, as well as its potentialities, will prove of inestimable value to the practitioner employ-

ing any of them. Elimination of pain, though the immediate aim of each, is only a means of reaching the final goal. This is to obtain a good obstetrical experience for the patient, safeguard the life and health of her baby, and lead to a happy, healthy, and well adjusted family. This goal is obtainable even when the techniques are adapted as adjuncts to the standard chemical methods of analgesia and anesthesia now in use. By using them in this fashion, their practical value will be greatly expanded.

The great disadvantages shared by these methods are the extra time and energy they require of the physician. These are not prohibitive, however, and with experience, they become a diminishing problem. At present, demands for psychophysiologic preparatory methods for childbirth are relatively small. It seems advisable to use them primarily for this small, motivated group of women who want them. At the same time, it is important to avoid their use for patients who are mentally unstable. The special case under psychiatric care for whom the psychiatrist recommends special psychophysiologic management is an exception. Best results are possible only if the techniques are used in formal fashion by physicians who understand the psychodynamics underlying the method to be used and who will take the extra time and effort that it requires. Only under these circumstances can results be good and unfortunate sequelae contained. Acceptance of these limitations will permit a true evaluation of the methods. If results are good, the demand for psychophysiologic techniques will increase. We think this will occur.

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# PHYSIOLOGY

PROCEEDINGS OF

## The Physiological Society of Philadelphia

SEMINAR ON ENVIRONMENTAL PHYSIOLOGY

SESSION OF NOVEMBER 15, 1960

**Pathophysiological Problems in Atmospheric Pollution.** HEINRICH BRIEGER, M.D. (Department of Preventive Medicine, Jefferson Medical College of Philadelphia). Air pollution hazardous to plant, animal, and human health is an extremely complex problem. Much has been learned from the investigation of industrial conditions. Exposure to community air pollution, however, is not limited to a work day, and a vast mixture of contaminants in low concentrations is involved. "Smog" is indeed a persistent mixture of gases and particulate matter (aerosols), producing new contaminants by interaction, adsorption, and sunlight. Acute episodes of very severe air pollution have caused many cases of fatal pulmonary disease, especially among very young and old people and people with cardiovascular disorders. The more permanent conditions in industrial regions, however, constitute a much larger problem. They differ from place to place because of varying local atmospheric and meteorologic conditions.

Many effects attributed to air pollution have been observed only in animal experiments. Carcinogenic action of polycyclic hydrocarbons is, at present, a matter of great concern rather than of knowledge. Olefins when irradiated in the presence of nitric oxide or nitrogen dioxide are believed to be the main cause of eye irritation, the most conspicuous effect of air pollution, but also formaldehyde, acrolein, and free radicals have been incriminated. Among the respiratory irritants, oxidants, especially ozone and its interaction products, seem to play an important role. Sources of oxidants are automobile exhaust fumes, sunlight, and static meteorologic conditions. $SO_2$ and $SO_3$ have been made responsible for respiratory irritation. Rather low concentrations of these agents, however, have been found repeatedly during periods of harmful air pollution. Synergistic interaction between vapors and aerosols; for example, metal oxides, explains this phenomenon. There is little evidence of synergistic action within the body.

Research dealing with the very low concentrations of potentially hazardous air pollutants cannot, in general, be directed at gross morphologic changes. Cardiopulmonary function studies have not been very enlightening so far. Investigations of subtle functional deviations, for example, of conditioned reflexes, activity, food intake, and the like, appear more promising.

**Discussion of Volume Methods to Protect Against Acceleration.** KENNETH R. COBURN, PH. D., PETER H. CRAIG, D.V.M.*, RUBEN F. GRAY, M.S., AND EDWARD L. BECKMAN, M.D. (Aviation Medical Acceleration Laboratory, U.S. Naval Air Development Center, Johns-

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ville, Pa.). In recent years considerable interest has been generated in regard to the use of water immersion as a means of protecting the human body against the inelastic distortions which accompany exposure to high acceleration loads. Early investigators reported a tremendous increase in the G tolerance of various aquatic invertebrates and vertebrates exposed while immersed in water. Small mammals were similarly exposed and showed increased tolerances, but of a lesser magnitude.

A man-carrying capsule was designed and evaluated using human subjects oriented in the transverse (prone) position at levels up to 31 G. This series of experiments deals with the physiological responses and pathological changes occurring in 14 adult chimpanzees exposed to 31 G while immersed in water in the positive (sitting) position.

From the experimental results it appears that, either with or without the introduction of pressurized air into the pulmonary system, overpressures develop in the lungs of sufficient magnitude to produce lung rupture and mediastinal emphysema. The hydrostatic pressure gradient developed in the water capsule under increased G loads brings about a cephalad migration of the air along fascial planes and large blood vessels.

**Genotype, Phenotype and Environment.** HAROLD F. BLUM (National Cancer Institute and Department of Biology, Princeton University). The degree of adaptation of organism to environment should be judged in terms of the degree of fit of all heritable overt aspects of the organism (phenotype), to the pertaining aspects of the environment. The algebraic sum of the degrees of fit would be an appropriate adaptive index, which should measure the success of competing genotypes in evolution by natural selection. To demonstrate adaptive advantage for an isolated phenotypic aspect would require not only detailed knowledge of the pertaining anatomy, physiology and environment, and their interrelationships; but of the relative fit of all other aspects of the phenotype to the environment as well. Example of the difficulty of obtaining such complete knowledge appears in the case of the melanin of human skin, which has been asserted to confer adaptive advantage by protecting against sunlight, and hence to have affected evolution of races. The effect of sunlight on the skin is complex, involving the spectral distribution of sunlight, as well as the spectral transmission and physiology of skin. Examined in terms of these factors* it appears that a high melanin content of the skin might have both advantages and disadvantages, the relative importance of which would be hard to determine. The attribution of an important role in evolution of human races to this substance seems not to be justified. Moreover, the geographical distribution of dark skin does not agree with the distribution of sunlight.

**Comparative Study of Temperature Regulatory Mechanisms in Primitive Man.** H. T. HAMMEL (Department of Physiology, University of Pennsylvania School of Medicine). Since 1958, several field teams have measured the thermal and metabolic responses of primitive men to moderate cold exposure. A discriminating test consists of measuring the oxygen consumption, the rectal temperature and several skin temperatures during an 8-hour exposure at night to a moderate cold stress (**P. F. Scholander, H. T. Hammel, K. Lange Andersen, Y. Loyning:** J. Appl. Physiol., **12**, 1, 1958). For the cold stress,

*For a discussion of these factors, see Blum, H. F., Does the Melanin of Human Skin have Adaptive Value? Quart. Rev. Biol. (in press).

the subjects rested or slept on a web cot inside a bag made of a single woolen blanket plus a thin wind cover at air temperatures between 0° and 5° C. The thermal and metabolic responses of several ethnic groups have been studied. These include: 1) the aborigines of Central Australia during the winter months (**P. F. Scholander, H. T. Hammel, J. S. Hart, D. H. Le Messurier, J. Steen:** J. Appl. Physiol., 13, 211, 1958), 2) the aborigines of Central and Northern (tropical) Australia during the summer months (**H. T. Hammel, R. W. Elsner, D. H. Le Messurier, H. T. Andersen, F. A. Milan:** J. Appl. Physiol., **14**, 605, 1959), 3) the Lapps of Finmark during the winter months (**K. Lange Andersen, Y. Loyning, J. D. Nelms, O. Wilson, R. H. Fox, A. Bolstad:** J. Appl. Physiol., **15**, 649, 1960), 4) the Indians of Old Crow, Yukon Territory in the autumn (**L. Irving, K. Lange Andersen, A. Bolstad, R. W. Elsner, J. A. Hildes, Y. Loyning, J. A. Nelms, L. J. Peyton, R. D. Whaley:** J. Appl. Physiol., **15**, 635, 1960), 5) the Old Crow Indians in the spring (**R. W. Elsner, K. Lange Andersen, L. Hermansen:** J. Appl. Physiol., **15**, 659, 1960), 6) the Alacaluf Indians of Southern Chile in the winter (**H. T. Hammel, R. W. Elsner, K. Lange Andersen, P. F. Scholander, C. S. Coon, A. Medina, L. Strozzi, F. A. Milan, R. J. Hock:** WADD Technical Report, 1961) as well as unacclimatized Europeans who were controls in most of the above studies. Three patterns of response were found: a) the unacclimatized European starts the period of cold exposure with a metabolic rate at or near a basal level and increases it markedly as his body temperature falls, b) the Central Australian aborigine starts with a metabolic rate near basal and slides slowly downward as his rectal and skin temperatures fall to a little lower values than those of the European, and c) the Alacaluf Indian starts with a high metabolic rate which declines slightly while his rectal temperature falls about as much, the skin temperatures of the trunk fall a little more, and the foot temperature falls a little less than the white subject's temperatures. The response of the Old Crow Indian was similar to that of the Alacaluf Indian while the response of the tropical Australian aborigine and the Lapp reindeer herder was intermediate between the response of the European and the Australian aborigine.

# BOOK REVIEWS AND NOTICES

HEART SOUNDS AND MURMURS, A CLINICAL PHONOCARDIOGRAPHIC STUDY. By P. A. ONGLEY, Consultant in Pediatrics, Mayo Clinic, HOWARD B. SPRAGUE, Board of Consultation, Massachusetts General Hospital, M. B. RAPPAPORT, Former Head of Department of Electrophysiologic Research, Sanborn Co., and A. S. NADAS, Cardiologist, Childrens Hospital, Boston. Pp. 360; 211 ills. New York: Grune & Stratton, Inc., 1960. Price, $9.75.

AUSCULTATION of the heart and the graphic registration of heart sounds have become increasingly important in the new era of cardiology. Though new techniques are available to provide precise information with respect to alterations in the physiology of the circulation, these simpler methods supply information not otherwise available, and often of vital significance in diagnosis. The more frequent use of phonocardiography in recent times has greatly aided the understanding of auscultatory phenomena and has made the stethoscope a more useful instrument. With the newer knowledge it is now often possible for the physician, without machine aids, to obtain diagnostic information which would have seemed beyond reach formerly.

Undoubtedly it is these facts that have accounted for the considerable number of new books on auscultation and sound recording that have been published recently. The present volume is another good one. It contains an excellent early section dealing with the physical principles involved, a field in which Rappaport and Sprague have made many important contributions. The remaining five sections are concerned with normal and abnormal sounds and murmurs. Good illustrations make possible a comprehension of the relationship of these sounds and murmurs to events in the cardiac cycle, both in the normal and in the diseased heart. The physician not versed in cardiac auscultation (unfortunately there are far too many who are not) would do well to read and study this book. T.D.

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RESUSCITATION OF THE NEWBORN INFANT. Edited by HAROLD ABRAMSON, M.D. Pp. 274; 36 ills. St. Louis: C. V. Mosby Company, 1960. Price, $10.00.

THE remarkable decrease in maternal mortality during recent years has been paralleled by a corresponding fall in infant deaths. It is not difficult to understand this when one realizes how easily the fetus in utero can be damaged by interrupting its oxygen supply and how vulnerable it is during delivery and the first few days of its extrauterine existence. A substantial proportion of maternal complications such as toxemia, abruptio placentae, prolonged and difficult labor and infection contribute to fetal hypoxia, which if prolonged can lead to extensive damage or even death.

"Resuscitation of the Newborn Infant," which was prepared by a Special Committee on Infant Mortality of the Medical Society of the County of New York, is intended to supply detailed information concerning the physiology of intrauterine existence and the prevention and management of anoxia. The contributors are obstetricians, pediatricians, anesthesiologists, physiologists and statisticians who are interested in and concerned with this particular problem. The information, therefore, is authoritative.

The material is presented in 17 chapters which include discussions of the basic problem of fetal anoxia, fetal physiology and pathology, obstetric problems associated with infant hypoxia, analgesia and anesthesia, resuscitation of newborn infants, the management of babies in the newborn nursery, laboratory studies and a final chapter devoted to varied methods by which the problem can be attacked in the future. The editor, Harold Abramson, has done a skillful job in coordinating the various aspects of the report.

This book is particularly valuable for those who are immediately responsible for the welfare of infants during labor and the neonatal period and it should be studied by obstetricians, anesthesiologists and pediatricians. Simple practical and effective methods for resuscitation are described in detail and specific directions are given concerning delivery room and nursery equipment which is necessary for proper management of affected infants. The material is presented in an interesting, easily readable style and the text is well illustrated by photographs, charts, tables and line drawings. J.W.

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SURGICAL DISEASES OF THE PANCREAS. By JOHN M. HOWARD, M.D., Professor and Chairman, Department of Surgery, Hahne-

mann Medical College; and GEORGE L. JORDAN, JR., M.D., Associate Professor of Surgery, Baylor University College of Medicine. Nine contributors. Pp. 607; 199 ills. Philadelphia: J. B. Lippincott Company, 1960. Price, $20.00.

PANCREATIC diseases, exclusive of diabetes, have been given comprehensive consideration. The book has twenty-five chapters. Five chapters are devoted to a historical sketch, surgical anatomy, embryology and congenital anomalies, physiology of external secretion, and the laboratory diagnosis of pancreatic disease. Separate chapters are given to meconium ileus and pancreatic trauma. Twelve chapters give detailed consideration to pancreatitis in all of its clinical aspects. In four chapters, pancreatic cysts, hyperinsulinism and islet cell tumor, ulcerogenic tumors, and benign and malignant tumors of the pancreas and peri-ampullary region are considered. Pancreatic resection and pancreatic fistula make up the final chapters.

Although the title of the book suggests the book would be of interest only to surgeons, it will have a much wider appeal. Basically, the book is a documentation of the authors' clinical experiences presented against the background of a comprehensive survey of the pertinent accumulated literature. As stated by the author ". . . we and our colleagues have attempted to provide a factual background, current and thoughtful, in which the opinions are based on the best observations available . . ."

To all those interested in the problems of pancreatic disease, both medical and surgical, this book presents a detailed, authoritative summation of our current knowledge. The bibliography is outstanding. The work should prove to be a definitive contribution in its field. V.L.

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ADVANCES IN INTERNAL MEDICINE. VOLUME X. Edited by WILLIAM DOCK, M.D., State University College of Medicine at New York City and I. SNAPPER, M.D., Beth-El Hospital, Brooklyn. Pp. 390; 63 ills. Chicago: Year Book Publishers, Inc., 1960. Price, $10.50.

As in previous years, this volume contains an excellent assortment of chapters presenting up-to-date summaries of important topics. There is, first, a review of the surgical treatment of mitral and aortic stenosis by Charles Baker of Guy's Hospital, London. Then comes a chapter on newer diagnostic techniques in congenital heart disease by Braunwald and Morrow of the National Heart Institute. This is followed by a discussion of the indications for and results of surgical treatment of congenital heart disease, by Maurice Campbell of Guy's. The fourth and fifth chapters deal with the gastrointestinal tract, the former with endocrinologic factors in the pathogenesis of peptic ulcer, and the latter with the malabsorption syndromes. The topics of the last five chapters are: Clinical Phonocardiography; Diagnosis and Management of the Curable Forms of Hypertension; Cushing's Syndrome: Experience with Total Adrenalectomy; The Control of Erythropoiesis; and Bronchiolo-Alveolar Carcinoma. The authors of all of these chapters have been wisely selected.

It is unfortunate that Drs. Horwith and Stokes in the chapter on Cushing's Syndrome apparently advocate perirenal air insufflation for diagnosis. They seem to be unaware of the fact that practically every outstanding clinic in the country has abandoned this procedure because of the common occurrence of air embolism deaths, even with the best technique. Some have luck for a while, but, sooner or later, the axe falls! Dr. Grob in the chapter on curable forms of hypertension mentions the danger of air embolism and advocates the presacral route, being unaware apparently of the increasing number of deaths being reported from air injected by this route. He is in agreement with the reviewer that the findings by any technique are very likely to be misleading.

The chapter on clinical phonocardiography is recommended especially to general practitioners. It is true that they will not be using the graphic technique in their practice, but an understanding of the classical findings by this method improves auscultatory comprehension immeasurably. Even in this day of complicated diagnostic machinery, the stethoscope remains an indispensible instrument, and it is unfortunate that cardiac auscultation is generally so poorly understood. Next to examination of the nervous system, this is probably the poorest part of most doctor's physical examination techniques. T.D.

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THE PLASMA PROTEINS. VOL. 1. ISOLATION, CHARACTERIZATION AND FUNCTION. Edited by FRANK W. PUTNAM. Pp. 420; 34 ills. New York: Academic Press, Inc., 1960. Price, $12.50.

THIS is the first of two volumes which undertake to present an "authoritative, interpretative, and integrated account of the plasma proteins, both for the individual

purified components and as a dynamic system." In this volume the plasma proteins are considered as a physicochemical system, and the isolation and characterization of the major components are described as well as their functional differentiation.

The first sections give the results of studies of plasma proteins by various methods, including precipitation, electrophoresis, ultracentrifugal analysis, and chromatography. The chemical composition and molecular parameters of purified plasma proteins are next considered, followed by discussions of albumin, globulin and antibodies, macroglobulins and high molecular weight antibodies, glycoproteins, and metal-binding plasma proteins and cation transport.

All of the chapters are written by experts who are actively working in the respective areas which they discuss. This is an excellent treatise which will be a valuable information source for biochemists, nutritionists, hematologists, immunologists, clinical investigators and others concerned with these important components of the blood. C.Z.

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FUNDAMENTALS AND POSSIBILITIES IN ANTI-TUBERCULOSIS VACCINATION. BY RICHARD PRIGGE, Director of the State Institute for Experimental Therapy, Paul Ehrlich Institute, Frankfort am Main, and GÜNTHER HEYMANN. Scientific Member of the Institute. Pp. 108. Toronto: University of Toronto Press, 1960. Price, $5.00.

SINCE Koch's demonstration of the infectious cause of tuberculosis in 1882, innumerable attempts have been made to modify, prevent or treat the disease by various forms of vaccination. Much fundamental knowledge in the general fields of hypersensitivity, resistance and immunity has been derived from studies related to tuberculosis.

Methods of vaccination have included the use of fully virulent tubercle bacilli, killed bacilli, components or metabolic products of bacilli, and attenuated bacilli, chiefly BCG.

The authors have reviewed the voluminous literature, and conclude that no method of vaccination has proved satisfactory. Concerning BCG, which has been used in many millions of individuals, the authors state: "We consider a definite verdict on the value of BCG to be premature, and consider it essential to first carry out vaccinations that would make possible a *precise evaluation*." Every report favorable to BCG has been found "imprecise." The criteria for precision demanded by the authors probably cannot be attained with large numbers of people living in modern society. The future of vaccination, if any, lies in methods using antigenically active components of the tubercle bacillus; realizing that there is more than one antigen.

The monograph contains a mass of information, an extensive bibliography and an index. It is not easy to read, retaining much of the character of its original German construction. It should prove valuable to students of immunology or tuberculosis, and to proponents or opponents of BCG vaccination.

R.C.

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AMINO ACIDS AND PEPTIDES WITH ANTIMETABOLIC ACTIVITY. Edited by G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch., AND CECILIA M. O'CONNOR, B.Sc. Pp. 286; illustrated. Boston: Little, Brown and Co., 1958. Price, $8.75.

THIS volume consists of the proceedings of a Ciba Foundation sponsored symposium on "Amino Acids and Peptides with Antimetabolic and Cytotoxic Properties" which was held in March, 1958. The same general format of other Ciba symposia was followed, with presentations by outstanding authorities and a recording of the ensuing discussions. Among the contributions to this meeting are: The mode of action of chloramphenicol; A preliminary study of the influence of amino acid deficiencies on experimental cancer chemotherapy; The interference of azaserine in purine biosynthesis; Clinical effects of amino acids carrying nitrogen mustard groups; Clinical and biological studies with actinomycins; Structure and function of some suphur-containing peptides; and Bacitracin.

For the most part the discussions are basically oriented. Those concerned with cancer chemotherapy at the laboratory or clinical level will find this an informative reference volume. C.Z.

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THE MOLECULAR BASIS OF EVOLUTION. BY CHRISTIAN B. ANFINSEN, National Heart Institute, National Institutes of Health, Bethesda, Md. Pp. 228; 99 ills. New York: John Wiley & Sons, Inc., 1959. Price, $7.00.

THE author, an outstanding biochemist, undertook an integrative study of protein chemistry and genetics in an effort to arrive at a better understanding of the fundamental forces which underlie the evolutionary process. This excellent book resulted from the stimulation engendered by the venture. His approach, which is necessarily broad in scope, can be appreciated from the chapter titles: The Time Scale and Some Evolutionary

Principles; Genes as Determinants of Heredity; The Chemical Nature of Genetic Material; The Substructure of Genes; Protein Structure; The Biologic Activity of Proteins in Relation to Structure; Species Variation in Protein Structure; The Accuracy of Protein Synthesis; Biosynthesis of Proteins; and Genes, Proteins, and Evolution.

A wealth of information has been condensed and lucidly presented in this small volume. It is recommended to all students of biology and medicine. C.Z.

---

WORK AND THE HEART. Edited by FRANCIS F. ROSENBAUM, M.D. AND ELSTON L. BELKNAP, M.D. Pp. 537; 46 ills. New York: Paul B. Hoeber, Inc., 1959. Price, $12.00.

CONFERENCES which bring together leading investigators in particular fields of scientific endeavor have become increasingly popular as a means of taking an inventory of the existing stock of knowledge and of the areas in which confusion or complete ignorance still prevails. Furthermore, the exchange of ideas between men working on closely related subjects often acts as a catalyst and leads to an accelerated advance of the frontiers of knowledge.

The present volume represents the transactions of such a conference, held in Milwaukee, Wis., and sponsored by the Wisconsin and American Heart Associations, the National Health Institute, and the Industrial Health Council of the A.M.A. The list of 76 participants includes such names as Biörck, Burch, Burchell, Dock, Edwards, Eichna, Katz, Keys, Sarnoff, Visscher, Warren and many other outstanding investigators. The book is divided into five sections: Basic Physiology, Clinical Physiology, Pathology, Work Classification, and Workmen's Compensation. The wide range of topics should prove to be of great value to basic scientists, internists and cardiologists. T.D.

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IMMUNO-PATHOLOGIE: CLINIQUE ET EXPÉRIMENTALE. BY P. MIESCHER AND K. O. VORLAENDER. Pp. 559; 119 ills. Paris: Editions Medicales Flammarion, 1959.

A NUMBER of outstanding European investigators have contributed to this French text on clinical and experimental immunopathology. The experimental section contains chapters on general immunology; auto-immunity; antibodies to erythrocytes, leukocytes, platelets, kidney, and liver; the immunologic aspects of tissue reactions in rheumatic disorders; and antibodies to nerve tissue. In the clinical section, topics dealt with include the acquired hemolytic anemias; disorders associated with leukocyte and thrombocyte antibodies; vascular purpura; the rheumatic diseases; thyroid disorders; systemic lupus erythematosus; demyelinating syndromes; anti-insulin antibodies; antibodies to ophthalmic tissues; and organ transplantation.

This is a good reference text and especially valuable as a guide to much European literature with which American workers may not be familiar. C.Z.

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STRESS AND CELLULAR FUNCTION. BY H. LABORIT, M.D. Pp. 255; 61 ills. Philadelphia: J. B. Lippincott Co., 1959. Price, $7.50.

THE renowned French surgeon-investigator, Laborit, has set forth in this book his views on resuscitation and on hibernation therapy. His approach is basically oriented, requiring knowledge and understanding of a number of biologic and physical disciplines. Cellular phenomena, organic phenomena, water and electrolyte balance, acid-base balance, and ionic and metabolic phenomena are among the areas discussed in connection with his concepts. Methods for the investigation and resuscitation of H ion excretory systems are next considered. The remaining pages are devoted to therapeutic approaches such as artificial hibernation, neuroplegia, hyperthermia and hypothermia which may be more rationally applied on the basis of the concepts presented.

Workers in surgical research will find this to be both a stimulating and provocative volume. It deserves serious consideration. C.Z.

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YEAR BOOK OF PEDIATRICS (1960-1961 SERIES). Edited by SYDNEY S. GELLIS, M.D., Professor of Pediatrics, Boston University School of Medicine. Pp. 479; 92 ills. Chicago: The Year Book Publishers, 1960. Price, $8.00.

THIS latest number of a valuable series accords with the high standards of the editor in previous volumes. The pediatric literature for the designated period is well represented and the abstracts, while concise, present the subjects in a remarkably complete and lucid manner. The usual editorial comments, prepared by numerous authorities, are of the highest order and aid the reader in the evaluation of the material selected. The index to both subjects and authors is complete and helpful. The book should be welcome for

all who wish a simple means of reviewing the high points of the pediatric literature throughout the world during the previous year. A.B.

---

PROGRESS IN EXPERIMENTAL TUMOR RESEARCH. Edited by F. HOMBURGER, M.D. Pp. 476; illustrated. Philadelphia: J. B. Lippincott Co., 1960. Price, $22.00.

THIS is the first of a projected series of periodic publications which will be devoted to monographic presentations of work in fast moving segments of experimental tumor research. The topics covered in the present volume include Experimental Virology of Cancer; The Polyoma Virus; Transmission of Human Leukemia to Mice; The Biochemical Aspects of Carcinogenesis; Tumor Enhancing Factors; Modifying Factors in Carcinogenesis; Cytotoxic Agents of the Purine and the Sterol Group; Oncolytic Antibiotics; Oncolytic Viruses; and Biochemistry of Tumors.

The authors are all actively engaged in the respective areas which they discuss. Thus, an authoritative, contemporary and timely progress report of the indicated subject matter is made available to the reader. Investigators in cancer research will find this a valuable reference work. C.Z.

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RADIATION THERAPY OF EARLY PROSTATIC CANCER. BY R. H. FLOCKS, AND D. A. CULP, M.D., State University of Iowa, Department of Urology, Iowa City, Iowa. Pp. 73; 40 ills. Springfield, Illinois: Charles C Thomas, 1960. Price, $4.50.

THIS monograph is an explicit and detailed work devoted entirely to the treatment of selected cases of cancer of the prostate by injection of radioactive Au 198 into the prostate gland. The handling of the radioactive material and technique for injection are fully discussed and illustrated.

The book is written from the surgeon's rather than a radio physicist's standpoint, and the authors emphasize the dependence of the clinician on the radioisotope expert for the latter considerations. K.C.

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Fuller, H. L.: Angiology *11*:200 (June) 1960.

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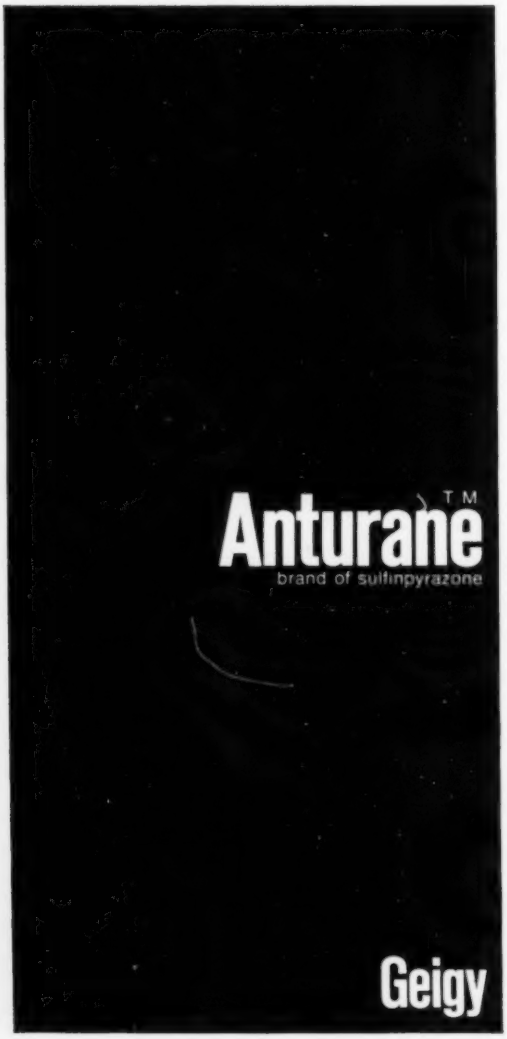


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References: 1. Seegmiller, J. E., and Grayzel, A. I.: J.A.M.A. 173:1076, 1960. 2. Yü, T. F., Burns, J. J., and Gutman, A. B.: Arth. & Rheumat. 1:532, 1958. 3. Kersley, G. D., Cook, E. R., and Towey, D. C. J.: Ann. Rheumat. Dis. 17:326, 1958. 4. Gutman, A. B., and Yü, T. F.: Bull. New York Acad. Med. 34:287, 1958.

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1. Nora, J. J.: M. Times, May, 1961. 2. Nora, J. J.: J.A.M.A. 174:113, Sept. 16, 1960. 3. Baer, S., et al.: J.A.M.A. 167:704, June 7, 1958. 4. Moser, K. M.: Disease-a-Month, Chicago, Yr. Bk. Pub., Mar., 1960, p. 13. 5. Meyer, O. O.: Postgrad. Med. 24:110, Aug., 1958.

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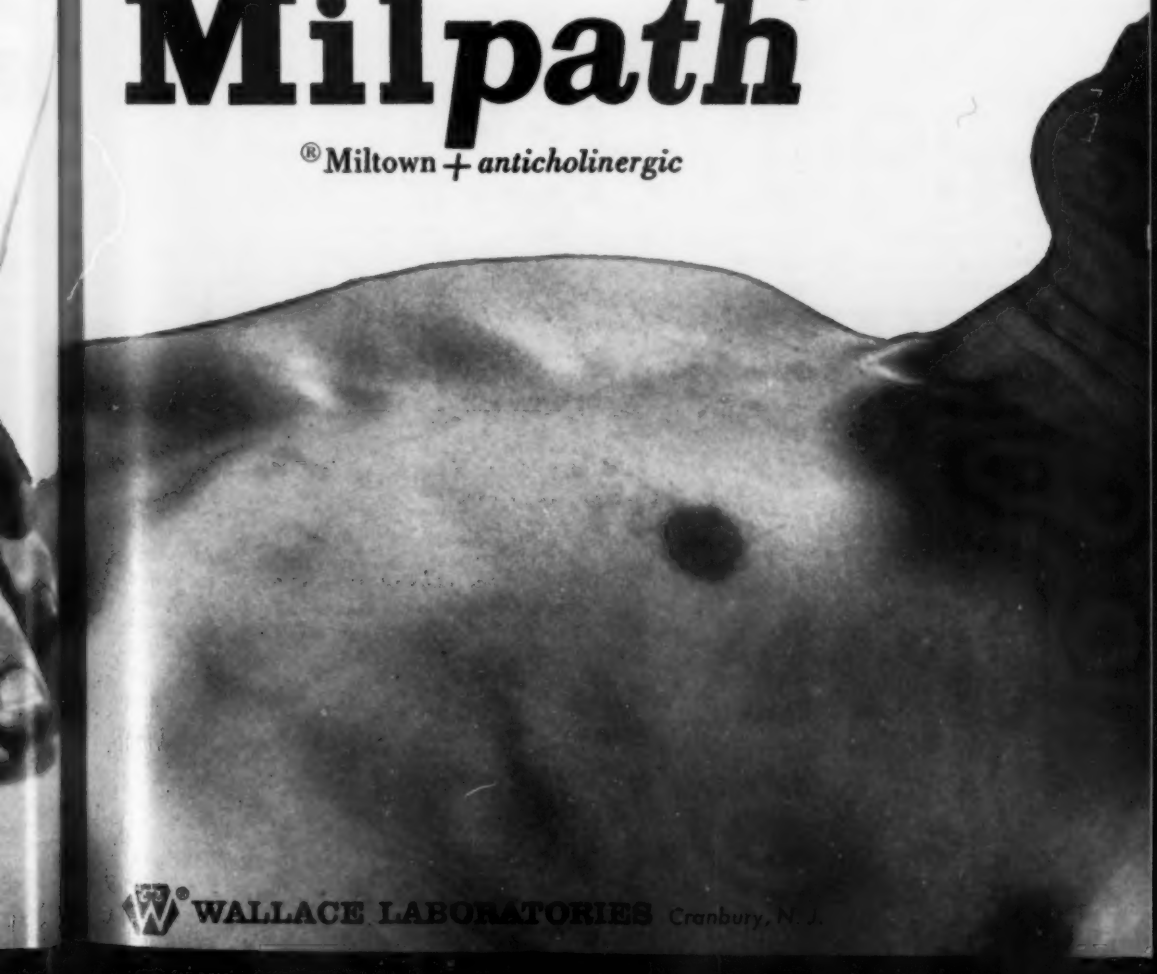

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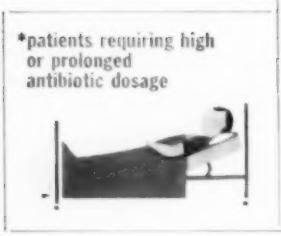

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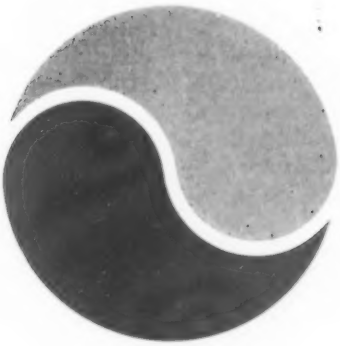

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References: 1. Ford, R. V.: Current Therap. Research **2**:347, 1960. 2. Fuchs, M., and others: Current Therap. Research **2**:[illegible], 1960. 3. Ford, R. V.: Connecticut Med. **24**:704-707, (Nov.) 1960. 4. Ford, R. V.: Texas State J. Med. **56**:343, 1960.
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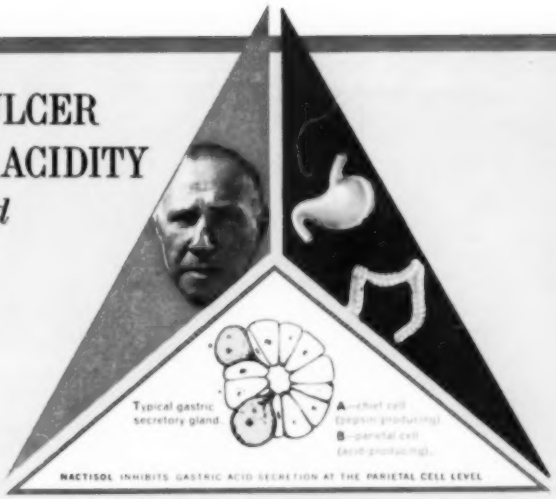
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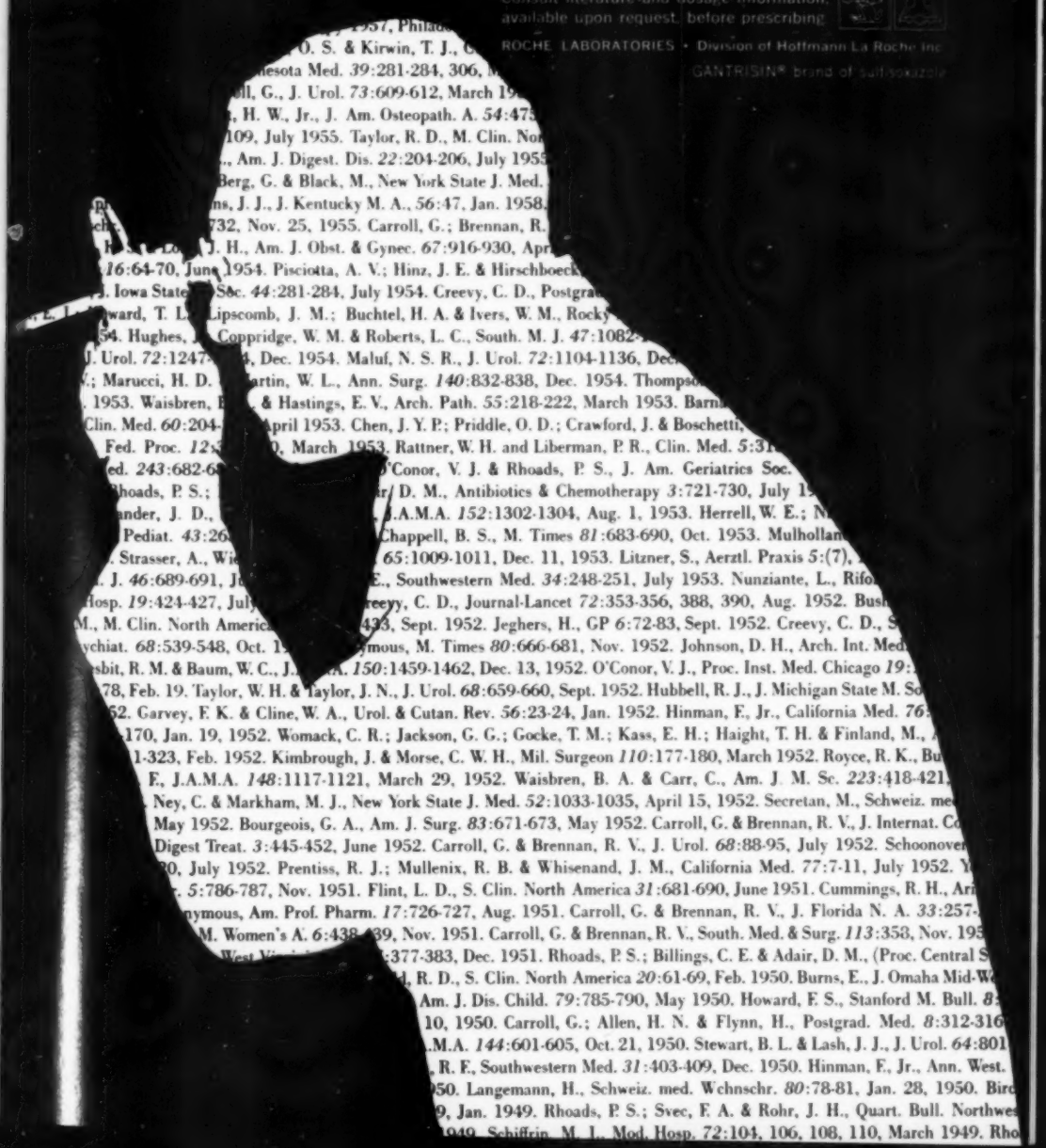

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# Proven

in over six years of clinical use and more than 750 published clinical studies

# Effective

for relief of anxiety and tension

# Outstandingly Safe

1. simple dosage schedule produces rapid, dependable tranquilization without unpredictable excitation
2. no cumulative effects, thus no need for difficult dosage readjustments
3. does not produce ataxia, change in appetite or libido
4. does not produce depression, Parkinson-like symptoms, jaundice or agranulocytosis
5. does not impair mental efficiency or normal behavior

# Miltown®

meprobamate (Wallace)

*Usual dosage:* One or two 400 mg. tablets t.i.d.
*Supplied:* 400 mg. scored tablets, 200 mg. sugar-coated tablets; in bottles of 50.

*Also supplied in sustained-release capsules . . .*

## Meprospan®

Available as Meprospan-400 (blue-topped *sustained-release* capsules containing 400 mg. meprobamate), and Meprospan-200 (yellow-topped *sustained-release* capsules containing 200 mg. meprobamate).

CM-4234

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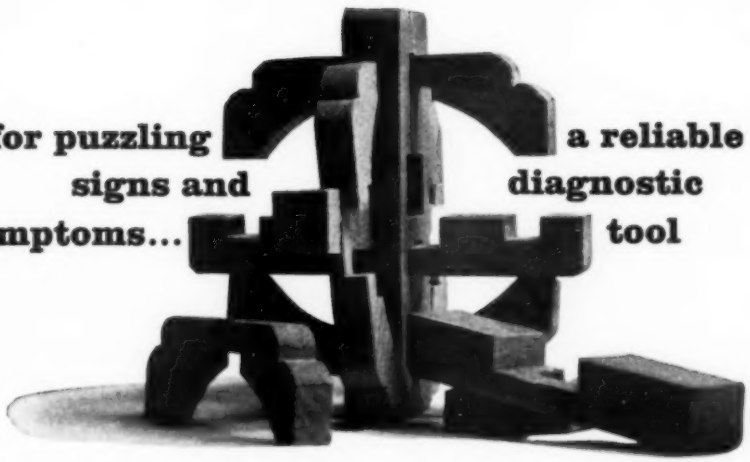

**for puzzling signs and symptoms...**

**a reliable diagnostic tool**

When signs and symptoms refuse to fall into place, the C.R.P.A. test accurately indicates inflammatory and necrotic diseases. A simple office procedure taking less than two minutes to set up and perform, the C.R.P.A. test can be used *prior to other tests* to determine the necessity for an erythrocyte sedimentation rate or SGO-T level.

Unlike the ESR or SGO-T level, a C.R.P.A. test demonstrates no variability in normal values. It is influenced only by the C-reactive protein in the patient's blood. A positive reaction always indicates pathology;[1] no false positives have ever been reported.

The C.R.P.A. test is a consistently constant indicator of acute myocardial infarction,[1-9] acute rheumatic fever,[10-12] active widespread malignant disease,[1,6,7,12,13] and bacterial infections.[1,5,7,14]

# C·R·P·A® *test*

## for routine blood chemistry

The reliability of the C.R.P.A. test makes it invaluable in differential diagnoses and routine work-ups. It may be used to deny or confirm ESR and SGO-T readings. Because it is so sensitive it can mark the progress of the disease and measure the effectiveness of therapy.[1,15]

**References:** 1. Editorial: J.A.M.A. 160:672 (Feb. 25) 1956. 2. Levinger, G. L.; Levy, H., and Elster, S. K.: Ann. Int. Med. 46:68, 1957. 3. Kroop, I. G., and Shackman, N. H.: Am. J. Med. 22:90, 1957. 4. Kroop, I. G., and Shackman, N. H.: Proc. Soc. Exper. Biol. & Med. 86:95, 1954. 5. Shubin, H.; Glaskin, A., and Heiken, C. A.: Tuberc. 15:62, 1955. 6. Losner, S., and Volk, B. W.: New York J. Med. 56:2665 (Sept. 1) 1956. 7. Roantree, R. J., and Rantz, L. A.: A.M.A. Arch. Int. Med. 96:674, 1955. 8. Goldner, F., and Meador, C.: South M. J. 48:1339, 1955. 9. Hedlund, P.: Acta med. scandinav. supp. 196:579, 1947. 10. Shackman, N. H.; Heffer, E. T., and Kroop, I. G.: Am. Heart J. 48:599 (Oct. 13) 1954. 11. Boland, E. W.: California Med. 82:65, 1955. 12. Knights, E. M., Jr.; Hutchins, M.; Morgan, E., and Ploompuu, J.: J.A.M.A. 162:9 (Sept. 1) 1956. 13. Shetlar, M. R.; Bullock, J. A.; Shetlar, C. L., and Payne, R. W.: Proc. Soc. Exper. Biol. & Med. 88:107, 1955. 14. Ruggieri, P. A.: J. M. Soc. New Jersey 52:500, 1955. 15. Dodd, K.: Mississippi Doctor 33:59, 1955.

*Complete literature and bibliography available on request.*

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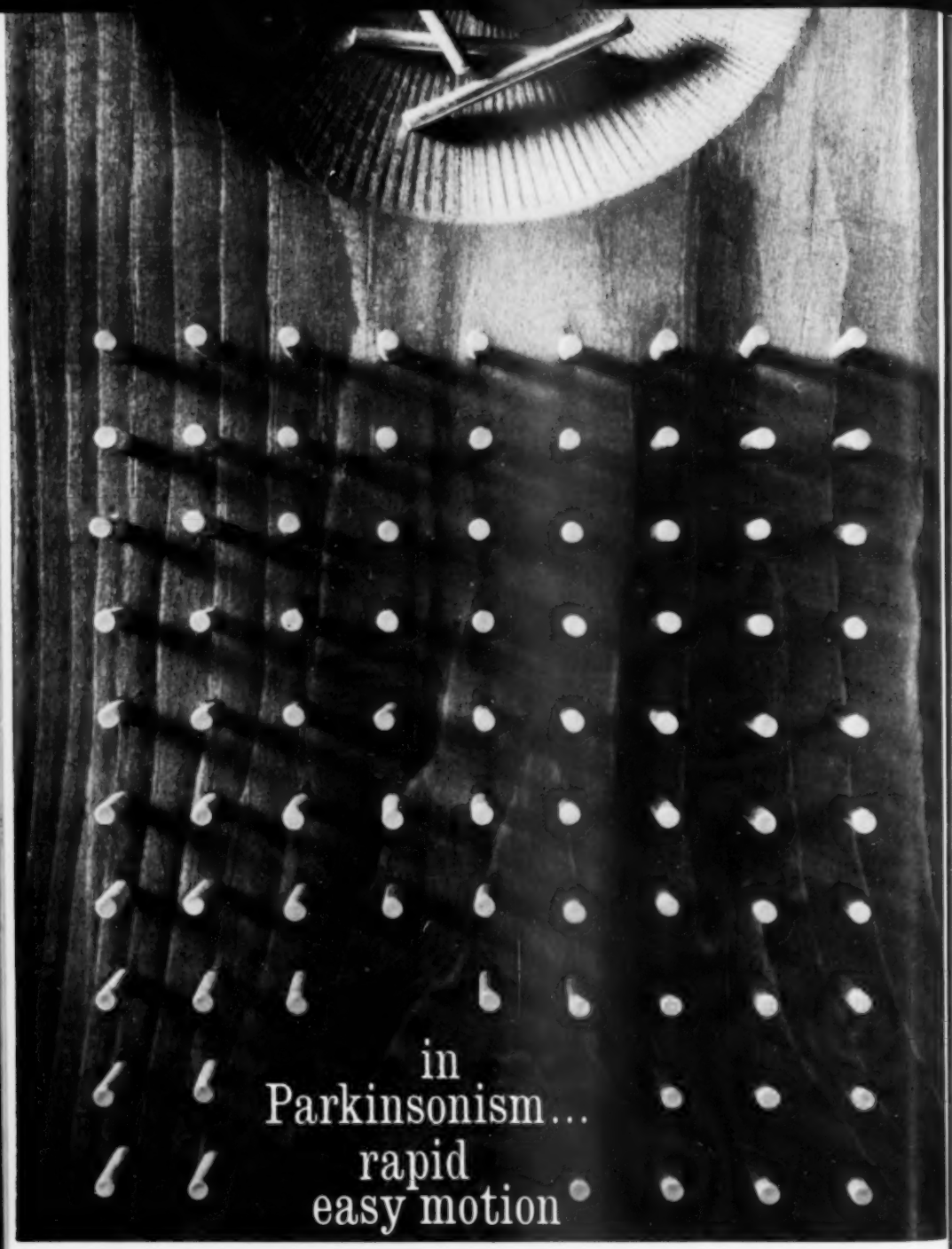


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Trihexyphenidyl HCl Lederle

*Request complete information on indications, dosage, precautions and contraindications from your Lederle Representative or write to Medical Advisory Department*

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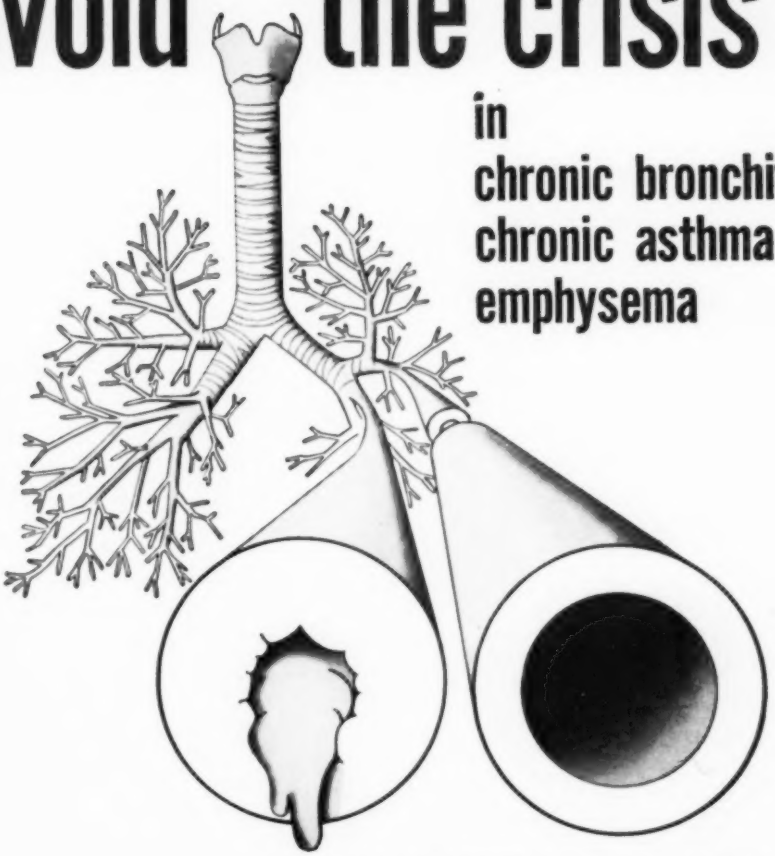
# to avoid the crisis

## in
## chronic bronchitis
## chronic asthma
## emphysema



**Choledyl provides uniformly effective bronchodilatation** throughout long-term therapy. Taken regularly, Choledyl helps prevent severe flare-ups in patients with chronic respiratory disease (the aging in particular) by affording continuous relief from debilitating bronchospasm. Gastric irritation and other unwanted effects are rare.

# CHOLEDYL®

THE CHOLINE SALT OF THEOPHYLLINE

brand of oxtriphylline

## keeps the airways open

*Supplied:* 200 mg. tablets (yellow), bottles of 100. *Precautions:* Side effects have been minimal but may include CNS stimulation or, rarely, palpitation. *Full dosage information, available on request, should be consulted before initiating therapy.*

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MORRIS PLAINS, N.J.

makers of Tedral Gelusil Proloid Peritrate Mandelamine

9P12

Maximal bending before medication

ROBAXIN Injectable administered

Dramatic improvement 15 minutes later

**Factual Clinical Data:** Male patient with marked spasm of right lumbar region found even slight bending extremely painful. Fifteen minutes after administration of 10 cc. of ROBAXIN Injectable, spasm had disappeared and patient could bend without pain. Photographs used with permission of patient.

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# In a matter of minutes

**"excellent" relief[4,10] in skeletal muscle spasm with**

# Robaxin

**INJECTABLE** Methocarbamol Robins U.S. Pat. No. 2770649

- "... subjective relief of pain usually begins within ten minutes ..."[10]
- "... a valuable therapeutic agent for the treatment of acute disorders involving skeletal muscle spasm."[4]
- "... effective in producing immediate relaxation of paravertebral muscle spasm in patients who have undergone cervical and lumbar laminectomies."[9]

# ...for continuing relief without drowsiness

# Robaxin

**TABLETS** Methocarbamol Robins

Ten published studies with 474 patients show ROBAXIN Injectable and ROBAXIN Tablets beneficial in 89% of cases.[1-10]

- "... a superior skeletal muscle relaxant in acute orthopedic conditions."[1]
- "An excellent result, after methocarbamol administration, was obtained in all patients with acute skeletal muscle spasm."[6]
- "In no instance was there decrease in intellect of simple reflex responses or voluntary muscle strength."[7]

Supply: ROBAXIN Injectable, 1.0 Gm. methocarbamol in 10-cc. ampul. ROBAXIN Tablets, 0.5 Gm. (white, scored) in bottles of 50 and 500.

Also available, for oral use when severe pain accompanies skeletal muscle spasm: ROBAXISAL Tablets (Robaxin with Aspirin) in bottles of 100 and 500. ROBAXIN-V.P. (Robaxin with Phenaphen®) in bottles of 100 and 500.

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Making today's medicines with integrity ... seeking tomorrow's with progress

# WHEN SPASM HAS 'EM

# BUTIBEL®

**co-ordinates antispasmodic/sedative action for smooth therapeutic control**

**BUTIBEL** offers an important clinical refinement in the relief of gastro-intestinal spasm... co-ordination of the reliable antispasmodic and antisecretory activity of Ext. belladonna 15 mg. and the intermediate sedative action of BUTISOL SODIUM® butabarbital sodium 15 mg.

**no "cumulative sedative drag"** Since these two components have essentially the same duration of action, **BUTIBEL** makes possible an even, time-matched therapeutic continuity for balanced control of both tension and spasm, without the "cumulative drag" so many patients experience with phenobarbital.

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more doctors are prescribing—

more patients are receiving the benefits of—

more clinical evidence exists for—

# DIURIL®

CHLOROTHIAZIDE

## than for any other diuretic-antihypertensive

**DIURIL** is unique. There is no other brand of chlorothiazide.

**Dosage:** Edema—One or two 500-mg. tablets DIURIL once or twice a day. Hypertension—One 250-mg. tablet DIURIL or one 500-mg. tablet DIURIL two to three times a day.

**Supplied:** 250-mg. and 500-mg. scored tablets DIURIL chlorothiazide in bottles of 100 and 1000.

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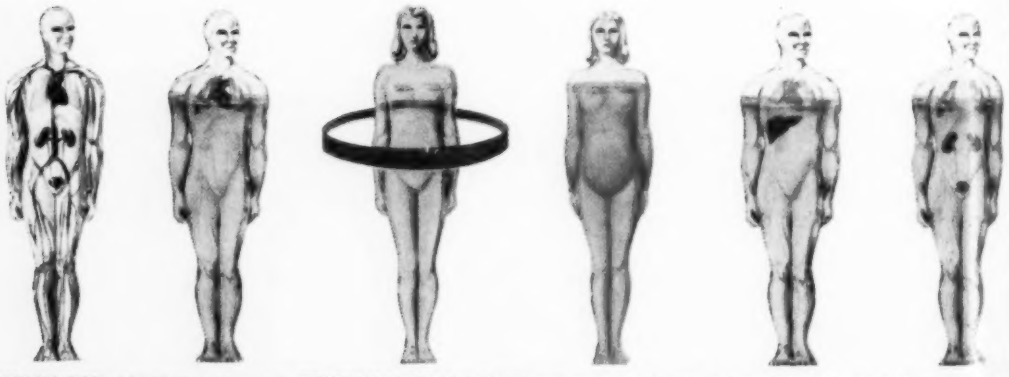

HYPERTENSION CONGESTIVE FAILURE PREMENSTRUAL TENSION EDEMA OF PREGNANCY CIRRHOSIS WITH ASCITES RENAL EDEMA

# 135 tiny doses mean smoother steroid therapy...

# in acute allergic disorders:

In the relatively acid medium of the fasting stomach, Medrol Medules remain essentially intact —**only 5% of the Medrol content is released after 2 hours at pH 1.2.** However, in the environment of the duodenum (approaching a pH of 7.5), **from 90 to 100% of the Medrol is released over a period of 4 hours.**

Judged to be "a nearly ideal formulation,"[1] Medrol Medules gave good to excellent results in 25 of 28 children with various acute allergic disorders. "There were no serious side effects and minor complaints were reported in only two patients."[1] The author also found that "there is a definite advantage for Medrol Medules inasmuch as much smaller doses seem able to produce full clinical relief. . . ."[1]

*Indications and effects*

Medrol benefits (anti-inflammatory, anti-allergic, antirheumatic, antileukemic, anti-hemolytic) have been demonstrated in acute rheumatic carditis, rheumatoid arthritis, asthma, hay fever and allergic disorders, dermatoses, blood dyscrasias, and ocular inflammatory disease involving the posterior segment.

*Precautions and contraindications*

Because of Medrol's high therapeutic ratio, patients usually experience dramatic relief *without* developing such possible steroid side effects as gastrointestinal intolerance, weight gain or weight loss, edema, hypertension, acne, or emotional imbalance.

As in all corticotherapy, however, there are certain cautions to be observed. The presence of diabetes, osteoporosis, chronic psychotic reactions, predisposition to thrombophlebitis, hypertension, congestive heart failure, renal insufficiency, or active tuberculosis necessitates careful control in the use of steroids. Like all corticosteroids, Medrol is contraindicated in patients with arrested tuberculosis, peptic ulcer, acute psychoses, Cushing's syndrome, herpes simplex keratitis, vaccinia, or varicella.

1. Dugger, J. A.: J. Michigan M. Soc. 59:1812 (Dec.) 1960.

# Medrol* Medules†

**Each capsule contains: Medrol (methylprednisolone) 4 mg.**

**Supplied in bottles of 30 and 100.**

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**The Upjohn Company**
**Kalamazoo, Michigan**

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# now...prolonged antipruritic action in a chewable tablet

## for chickenpox and other pruritic conditions

new...unique...pleasant-tasting

# tacaryl® T.M.

## chewable tablets

METHDILAZINE, MEAD JOHNSON

prolonged antipruritic/antiallergic action...
not dependent on delayed intestinal release

**Itching in children can now be controlled on b.i.d. dosage with a long-acting[1] antipruritic/antiallergic chewable tablet your pediatric patients will enjoy taking.**

Tacaryl Hydrochloride is exceptionally valuable in alleviating many types of allergic and non-allergic pruritus. For example, in a group of children, 2 to 12 years of age, with atopic dermatitis, chickenpox, or contact dermatitis, 80 per cent obtained substantial or complete relief of their itching when treated with Tacaryl Hydrochloride. "No patient in this age group failed to show some degree of improvement."[2]

Tacaryl Hydrochloride is also effective in controlling symptoms in a wide variety of allergic conditions,[2-8] including hay fever and perennial rhinitis.

**dosage:** One Chewable Tablet (3.6 mg.) twice daily. Adjustment of dose or interval may be desirable for some patients.

**contraindications:** There are no known contraindications.

**side effects:** Drowsiness has been observed in a small percentage of patients. Dizziness, nausea, headache, and dryness of mucous membranes have been reported infrequently.

**cautions:** If drowsiness occurs after administration of Tacaryl Chewable Tablets or Tacaryl Hydrochloride, the patient should not drive a motor vehicle or operate dangerous machinery. Since Tacaryl Chewable Tablets or Tacaryl Hydrochloride may display potentiating properties, it should be used with caution for patients receiving alcohol, analgesics or sedatives (particularly barbiturates). Because of reports that phenothiazine derivatives occasionally cause side reactions such as agranulocytosis, jaundice and orthostatic hypotension, the physician should be alert to their possible occurrence...though no such reactions have been observed with Tacaryl Chewable Tablets or Tacaryl Hydrochloride.

**supplied:** Pink tablets, 3.6 mg., bottles of 100.

**references:** (1) Lish, P. M.; Albert, J. R.; Peters, E. L., and Allen, L. E.: Arch. internat. pharmacodyn. *129*:77-107 (Dec.) 1960. (2) Howell, C. M., Jr.: North Carolina M. J. *21*:194-195 (May) 1960. (3) Clinical Research Division, Mead Johnson & Company. (4) Wahner, H. W., and Peters, G. A.: Proc. Staff Meet. Mayo Clin. *35*:161-169 (March 30) 1960. (5) Crepea, S. B.: J. Allergy *31*:283-285 (May-June) 1960. (6) Crawford, L. V., and Grogan, F. T.: J. Tennessee M. A. *53*:307-310 (July) 1960. (7) Spoto, A. P., Jr., and Sieker, H. O.: Ann. Allergy *18*:761-764 (July) 1960. (8) Arbesman, C. E., and Ehrenreich, R.: New York J. Med. *61*:219-229 (Jan. 15) 1961.

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# Protects the angina patient better than vasodilators alone

Unless the coronary patient's ever-present anxiety about his condition can be controlled, it can easily induce an anginal attack or, in cases of myocardial infarction, can delay recovery.

This is why Miltrate gives better protection for the heart than vasodilators alone in coronary insufficiency, angina pectoris and postmyocardial infarction.

Miltrate contains PETN (pentaerythritol tetranitrate), acknowledged as basic therapy for long-acting vasodilation. . . .

What is more important—Miltrate provi Miltown, a tranquilizer which, unlike phenobarbital, relieves tension in the apprehensive angina patient without inducing daytime fogginess.

Thus, your patient's cardiac reserve is protected against his fear and concern about his condition; his operative arteri are dilated to enhance myocardial blood supply—and he can carry on normal activities more effectively since his ment acuity is unimpaired by barbiturates.

**REFERENCES:** **1.** Ellis, L. B. *et al.:* Circulation *17*:945, May 1958. **2.** Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. **3.** Riseman, J.E.F.: New England J. Med. *261*:1017, Nov. 12, 1959. **4.** Russek, H. I. *et al.:* Circulation *12*:169, Aug. 1955. **5.** Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. **6.** Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. **7.** Waldman, S. and Peiner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

**Supplied:** Bottles of 50 tablets. Each tablet contains 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.

**Dosage:** 1 or 2 tablets q.i.d. *before meals* and at bedtime, according to individual requirements.

CML-3619

**Miltrate®**

Miltown® (meprobamate) + PETN

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ymes, and amino acids.

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7 mg. nicotinamide, 10 mg. *dl*-panthenol,
7 mg. choline bitartrate; minerals—
7 mg. ferrous sulfate (exsiccated), 0.05 mg.
ine (as potassium iodide), 66.7 mg.
ium carbonate; digestive enzymes—
mg. Taka-Diastase® (Aspergillus oryzae
ymes), 133.3 mg. pancreatin; amino
ds—66.7 mg. *l*-lysine monohydrochloride,
7 mg. *dl*-methionine; gonadal hormones—
7 mg. methyltestosterone, 0.167 mg. Theelin.
*age:* One Kapseal three times daily before
als. Female patients should follow each
day course with a 7-day rest interval.
*cautions:* Contraindicated in patients
erein estrogen or androgen therapy should
t be used, as in carcinoma of the breast,
ital tract, or prostate, and in patients
h a familial tendency to these types of
lignancy; give cautiously to females
o tend to develop excessive hair growth
other signs of masculinization.
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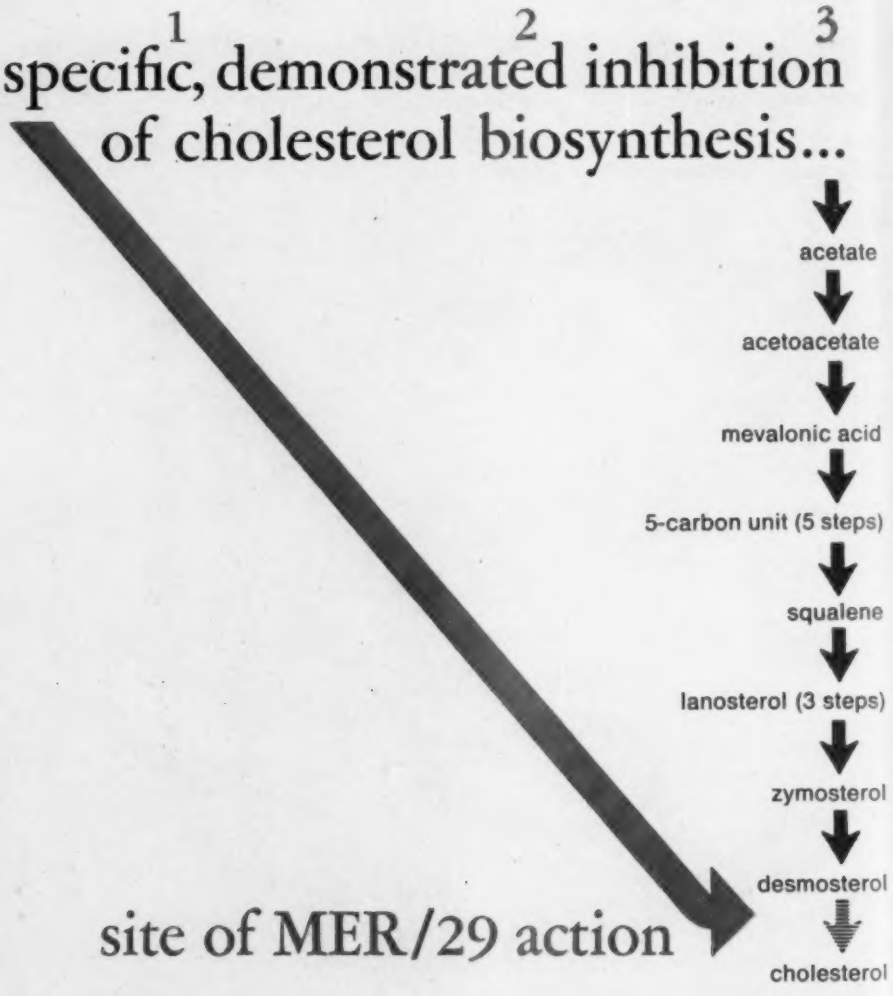


1. The primary, the *only* known action of MER/29 is to lower the total body pool of sterols (serum and tissue); no effect on any other system or organ reported to date.

2. "Using each patient as his own control, the peak *total* sterol radioactivity after injection of mevalonic acid-2-$C^{14}$ was compared on and off MER/29. As much as a 50 per cent inhibition on MER/29 was observed in some patients."
—Steinberg, D.; Avigan, J., and Feigelson, E. B.: Circulation *22*:663 (Oct.) 1960.

3. "Studies of lipid metabolism have stressed the importance of cholesterol biosynthesis, as opposed to cholesterol intake, in determining cholesterol balance."
—National Heart Institute: Diet, Hormones, and Atherosclerosis..., Bethesda, Md., U.S. National Institutes of Health, 1958.

# ...leading to specific, demonstrated advantages in cholesterol-lowering therapy

particularly in patients with coronary artery disease, generalized atherosclerosis, and other conditions thought to be associated with abnormal cholesterol metabolism

**MER/29 REDUCES CHOLESTEROL IN AS MANY AS 8 OUT OF 10 PATIENTS:** MER/29 reduces both serum and tissue cholesterol without strict adherence to diet. Although some physicians prefer to use MER/29 in conjunction with controlled diets, cholesterol can be reduced successfully without such limitation.

**CONCURRENT BENEFITS REPORTED IN SOME PATIENTS:** In patients with coronary artery disease, some of the concurrent benefits reported include decreased incidence and severity of anginal attacks, improved ECG patterns, diminished nitroglycerin dependence, and increased sense of well-being.

**MER/29 HAS PRODUCED FEW SIDE EFFECTS, NO TOXICITY:** Patients have been treated with MER/29 for continuous periods up to 19 months. In no case has there been evidence of serious toxic effects on the function of any vital organ or system. Side effects (nausea, headache, dermatitis) are rare and have usually been associated with dosages greater than those recommended for effective therapy.

MER/29 is compatible with other cardiovascular therapies. It can be used along with measures which control anxiety, hypertension, obesity and other conditions associated with cardiovascular disorders. These include nitroglycerin, PETN, and anticoagulants.

CAUTION: Since long-term MER/29 therapy may be necessary, periodic examinations, including liver function tests, are desirable. Also, since MER/29 inhibits cholesterol biosynthesis, and cholesterol plays an important role in the development of the fetus, the drug is *contraindicated in pregnancy.*

DOSAGE: One 250 mg. capsule daily, before breakfast.

SUPPLIED: Bottles of 30 pearl gray capsules.
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(triparanol)

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*Cincinnati, Ohio • Weston, Ontario*

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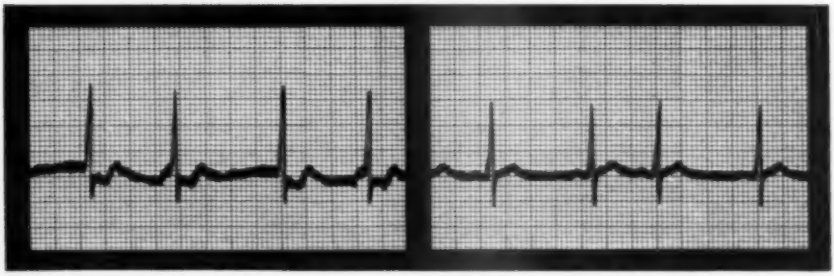
# coronary artery disease is not limited to angina

## . . . neither is Peritrate

In postcoronary patients with or without angina, Peritrate provides the benefits of substantial and sustained increase in myocardial blood flow **without significant change in cardiac output, blood pressure or pulse rate.**

electrocardiographic evidence in

**a patient with angina***

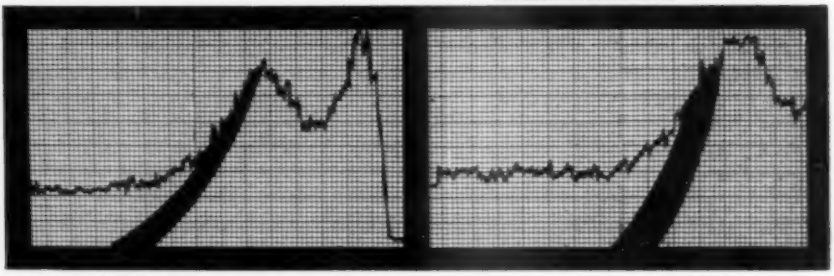


**Before Peritrate**—S-T segment depressed after standard exercise.

**After Peritrate** (20 mg. given 4 hours before exercise test) S-T segment now normal.

radioisotopic tracings of

**a postcoronary patient without angina***



**Before Peritrate**—Radioisotopic tracing shows reduced myocardial blood flow (shaded area) after infarction.

**After Peritrate** (20 mg. given 2½ hours before study) myocardial blood flow substantially increased.

Full dosage information, available on request, should be consulted before initiating therapy.

*Electrocardiograms, radioisotopic tracings and case histories on file in the Medical Department, Warner-Chilcott Laboratories

basic therapy in coronary artery disease
—with or without angina

GP14

**Peritrate®**

brand of pentaerythritol tetranitrate

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# STOPS THE ASTHMA ATTACK IN MINUTES...FOR HOURS... ORALLY

# ELIXOPHYLLIN®

**RAPID RELIEF IN MINUTES**—in 15 minutes[1,2,3] mean theophylline blood levels are comparable to I. V. aminophylline—so that severe attacks have been terminated in 10 to 30 minutes.[1,4,5,6]

**SUSTAINED RELIEF FOR HOURS**—After absorption theophylline is slowly eliminated during a 9-hour period,[7] making possible t.i.d. 'round-the-clock protection in chronic cases. **Note:** *With Elixophyllin the patient can learn to abort an attack in its incipient stage.*

**NO UNNEEDED SIDE EFFECTS**—Since Elixophyllin does not need "auxiliaries," it contains no ephedrine—no barbiturate—no iodide—no steroid. *Gastric distress is rarely encountered.*[8,9]

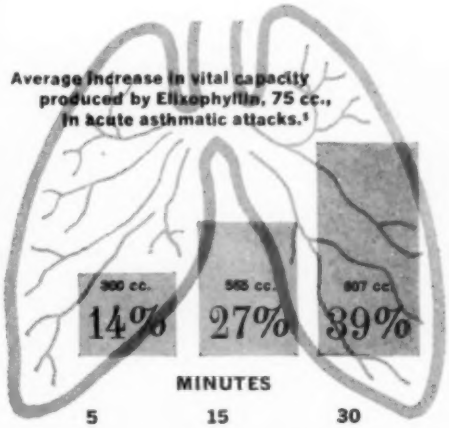
Each tablespoonful (15 cc.) contains theophylline 80 mg. (equivalent to 100 mg. aminophylline) in a hydro-alcoholic vehicle (alcohol 20%).

**ACUTE ATTACKS:**

single dose of 75 cc. for adults; 0.5 cc. per lb. of body weight for children.

**24 HOUR CONTROL:**

for adults 45 cc. doses before breakfast, at 3 P.M., and before retiring; after two days, 30 cc. doses. Children, first 6 doses 0.3 cc.—then 0.2 cc. per lb. of body weight as above.

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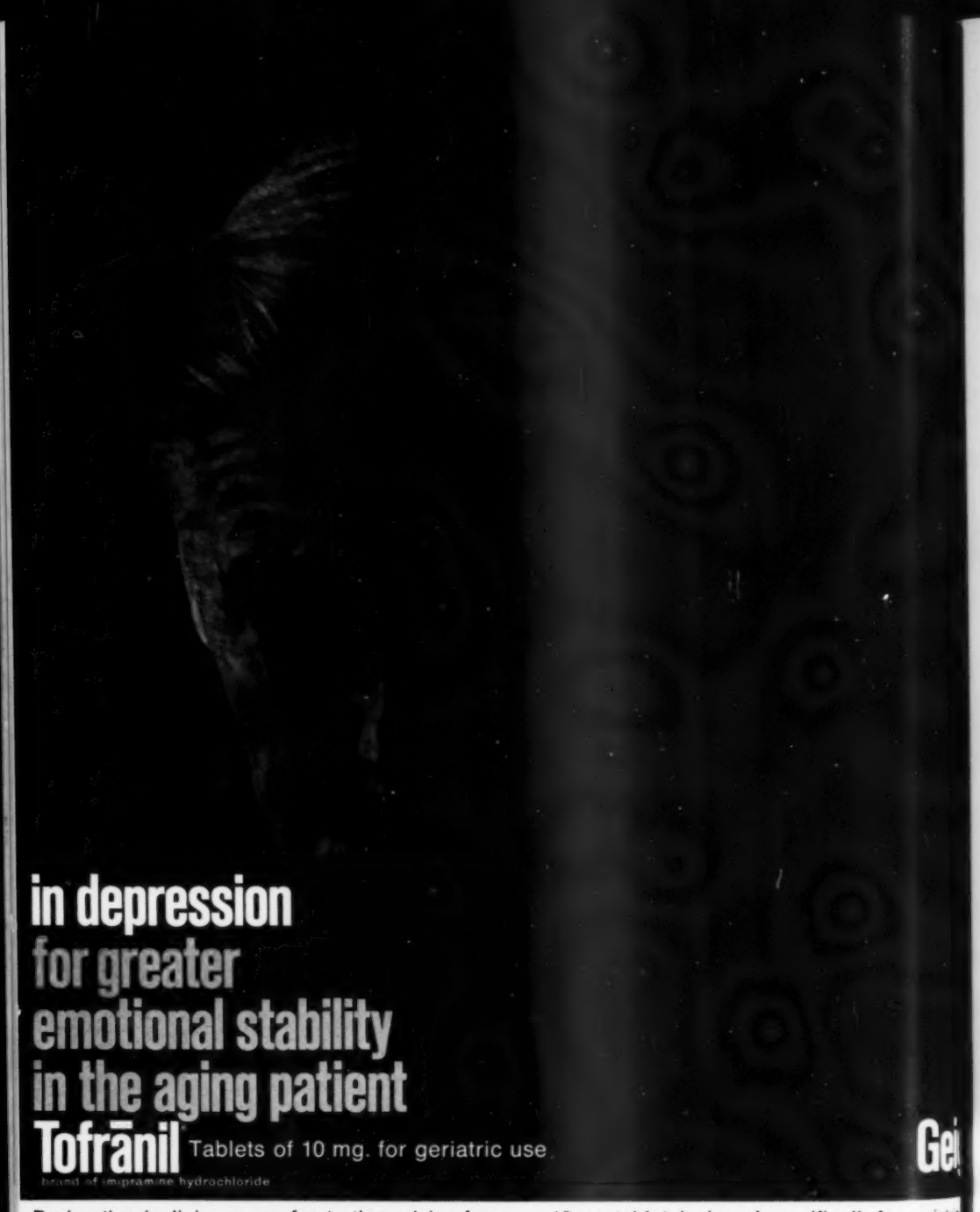

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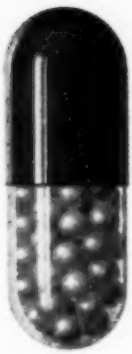

# in acute allergic disorders:

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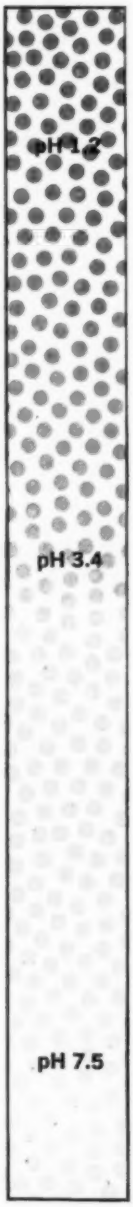


Judged to be "a nearly ideal formulation,"[1] Medrol Medules gave good to excellent results in 25 of 28 children with various acute allergic disorders. "There were no serious side effects and minor complaints were reported in only two patients."[1] The author also found that "there is a definite advantage for Medrol Medules inasmuch as much smaller doses seem able to produce full clinical relief. . . ."[1]

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Medrol benefits (anti-inflammatory, anti-allergic, antirheumatic, antileukemic, anti-hemolytic) have been demonstrated in acute rheumatic carditis, rheumatoid arthritis, asthma, hay fever and allergic disorders, dermatoses, blood dyscrasias, and ocular inflammatory disease involving the posterior segment.

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1. Dugger, J. A.: J. Michigan M. Soc. 59:1812 (Dec.) 1960.

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*PATIENTS WITH IMPENDING CARDIAC DECOMPENSATION*

In contrast to most of its congeners, ARISTOCORT is not contraindicated when edema is present or when cardiac decompensation impends.[1]

*PATIENTS WITH EMOTIONAL AND NERVOUS DISORDERS*

Triamcinolone did not produce psychic disturbances or insomnia.[2]

*PATIENTS WHOSE APPETITES SHOULD NOT BE STIMULATED*

Among patients treated with ARISTOCORT, there was less appetite stimulation, especially in those who had previously gained weight on long-term therapy with other steroids.[3]

*PATIENTS WITH HYPERTENSION*

There was no blood pressure increase in any patient treated for bronchial asthma, and in some, blood pressure fell. Of these, three had been hypertensive.[4]


*References:*

1. McGavack, T. H.; Kao, K. Y. T.; Leake, D. A.; Bauer, H. G., and Berger, H. E.: *Am. J. M. Sc.* 236:720 (Dec.) 1958.
2. McGavack, T. H.: *Nebraska M. J.* 44:377 (Aug.) 1959.
3. Friedlaender, S., and Friedlaender, A. S.: *Antibiotic Med. & Clin. Ther.* 5:315 (May) 1958.
4. Sherwood, H., and Cooke, R. A.: *J. Allergy* 28:97 (March) 1957.


*Precautions:* Collateral hormonal effects generally associated with corticosteroids may be induced. These include Cushingoid manifestations and muscle weakness. However, sodium and potassium retention, edema, weight gain, psychic aberration and hypertension are exceedingly rare. In the treatment of allergic respiratory disorders, dosage should be individualized and kept at the lowest level needed to control symptoms. Dosage should not exceed 36 mg. daily without potassium supplementation. Drug should not be withdrawn abruptly. Contraindicated in herpes simplex and chicken pox.

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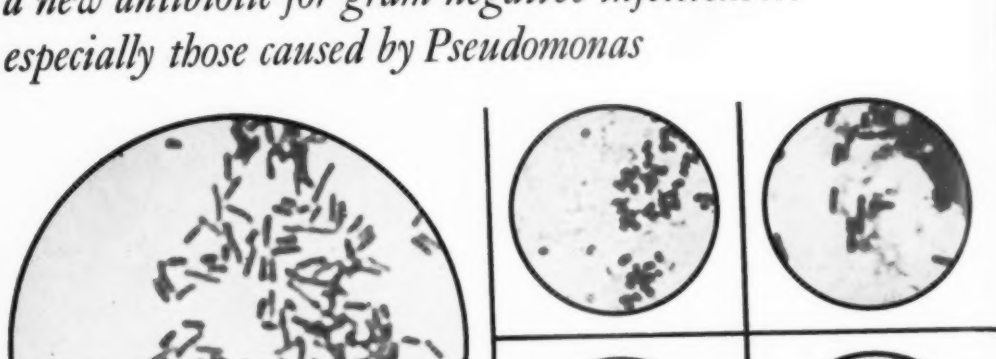

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*References:* 1. Carroll, G., and Malette, W. F.: J. Urol. *85*:86, 1961. 2. Petersdorf, R. G., and Hook, E. W.: Bull. Johns Hopkins Hosp. *107*:133, 1960. 3. Hall, J. W.: Am. J. M. Sc. *240*:561, 1960. 4. Zinsser, H. H.; Lattimer, J. K., and Seneca, H.: J. Urol. *83*:755, 1960. 5. Roberts, C. E., Jr., and Kirby, W. M. M.: Colistin in the treatment of hospitalized patients with Pseudomonas infections, presented at the 1960 Conference on Anti-Microbial Agents, Washington, D. C. 6. Schwartz, B. S., et al.: Antibiotics Annual 1959-1960, New York, Antibiotica, Inc., 1960, pp. 41-60. 7. Graber, C. D.; Tumbusch, W. T., and Vogel, E. H., Jr.: *Ibid.*, pp. 77-79. 8. Wright, W. W., and Welch, H.: *Ibid.*, pp. 61-74. 9. Ross, S.; Puig, J. R., and Zarem, E. A.: *Ibid.*, pp. 89-100. 10. McCabe, W. R.; Jackson, G. G., and Kotij, V. M.: *Ibid.*, pp. 80-88. 11. Blaustein, A.: *Ibid.*, pp. 75-76. 12. Meleney, F. L., and Prout, G. R.: Surg. Gynec. & Obst. *112*:211, 1961. 13. McCabe, W. R., and Jackson, G. G.: Am. J. M. Sc. *240*:754, 1960. 14. Carroll, G.: J. Oklahoma M. A. *53*:678, 1960. 15. Seneca, H.; Lattimer, J. K., and Zinsser, H.: New York J. Med. *60*:3630, 1960.

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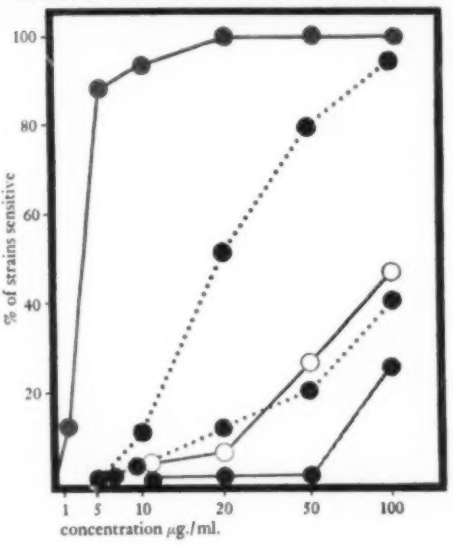


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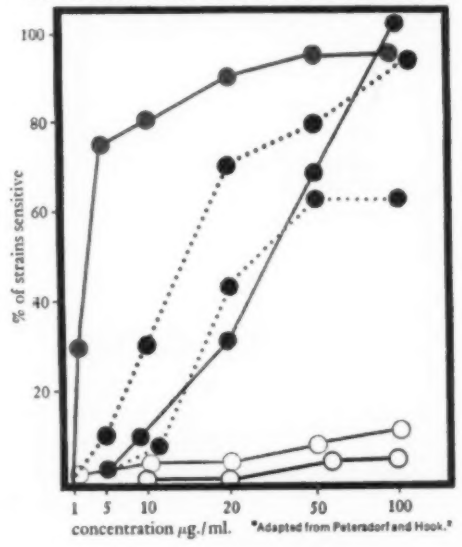


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# WHEN YOUR PATIENTS TAKE THEIR OWN BLOODPRESSURE

Ganglionic blocking agents and other hypotensive drugs, now widely used for the treatment of hypertension, are highly potent agents. They are safe only when dosages are regulated according to frequent bloodpressure determinations. Many physicians° find they can teach their patients to take their own bloodpressure and keep an accurate record. In this way dosages may be regulated with comparative safety.

If you are prescribing potent hypotensive drugs and want your patients to take their own bloodpressure at home, you will be interested in the Rx-ManometeRx$^{T.M.}$ — an accurate, mercury-gravity instrument for use under your supervision.

For these patients, the W. A. Baum Co. has made available the Rx-ManometeRx. This instrument, like all those made by the W. A. Baum Co., is a true mercury-gravity sphygmomanometer. The mercury displacement principle in bloodpressure measurement excludes the possibility of functional error in the instrument itself. The gravity principle provides the standard against which all other types of manometers must be calibrated and checked when their accuracy is in doubt.

Although a difference of a few millimeters in bloodpressure determinations may be of small moment, it is certainly not desirable to compound errors. Ten millimeters too low one day, and ten millimeters too high the next, leads to the important variation of 20 millimeters. With an accurate mercury-gravity instrument, like the Baumanometer, such errors, due to the instrument itself, are eliminated.

Whenever — wherever you take a reading with a Baumanometer you *know* it is accurate. That is why we say . . . TO BE SURE . . . prescribe a Baumanometer — standard for bloodpressure the world over.

*The* $31.95 *price* for Rx-ManometeRx is only slightly higher than the cheapest sphygmomanometer which your patients can buy. And a Baumanometer, built to give years of accurate, dependable service, is certainly *the best* they can buy.

When you want an accurate home record of your patient's bloodpressure, prescribe the Rx-ManometeRx. Available at your surgical instrument dealer.

°


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Baumanometer
BLOODPRESSURE STANDARD THE WORLD OVER

**W. A. BAUM CO., INC., COPIAGUE, L. I., N. Y.**

*Since 1916 Originator and Maker of Bloodpressure Apparatus Exculsively*

# and the fat recommendation in current dietary thinking

Cholesterogenesis in man is recognized as a highly complex process, only partially affected by the character of the diet. Nonetheless, the opinion is often expressed that the lipid content of the adult American diet might well be reduced from its current level of 40 to 50% of daily calories to about 30%.

The ultimate goal of this recommendation is the possible reduction of serum cholesterol levels.

Because eggs constitute an important part of protein, vitamin, and mineral nutrition, they are included in virtually every authoritative low fat diet. In a diet supplying 2500 calories, 30% of which are furnished by lipids, the lipids of two eggs comprise only 1/7 of the allowed daily fat intake.

**Two Eggs Provide*:**

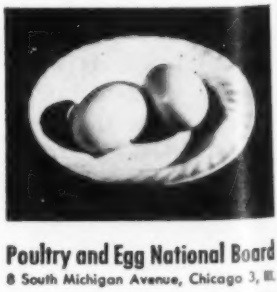
| | |
|---|---|
| Protein | 13 Gm. |
| Carbohydrate | 1 Gm. |
| Fats (total lipids) | 12 Gm. |
| Fatty acids | |
| Saturated (total) | 4 Gm. |
| Unsaturated | |
| Oleic acid | 5 Gm. |
| Linoleic acid | 1 Gm. |

Vitamins present: A, D, E, K, $B_1$, $B_2$, $B_6$, $B_{12}$, pantothenic acid, niacin, folic acid, biotin.

Minerals present: Calcium, phosphorus, sodium, potassium, chlorine, sulfur, iron, iodine, manganese, magnesium, zinc, copper.

**U. S. Department of Agriculture Home and Garden Bulletin No. 72, Sept. 1960.*

*The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.*



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8 South Michigan Avenue, Chicago 3, Ill.

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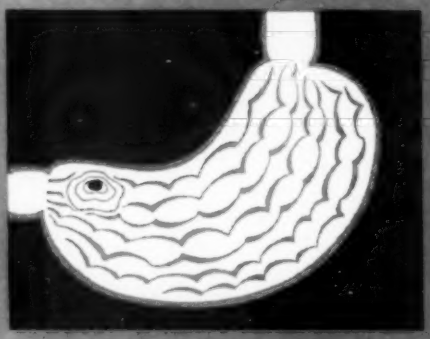
of

# Titralac*



for immediate and prolonged relief in peptic ulcer and hyperacidity

**Preferred for**

- potency
- immediate relief (within seconds)
- lasting effect
- milk-like action
- fresh mint flavor
- non-chalky smoothness
- freedom from effect on intestinal function

## TITRALAC® TABLETS

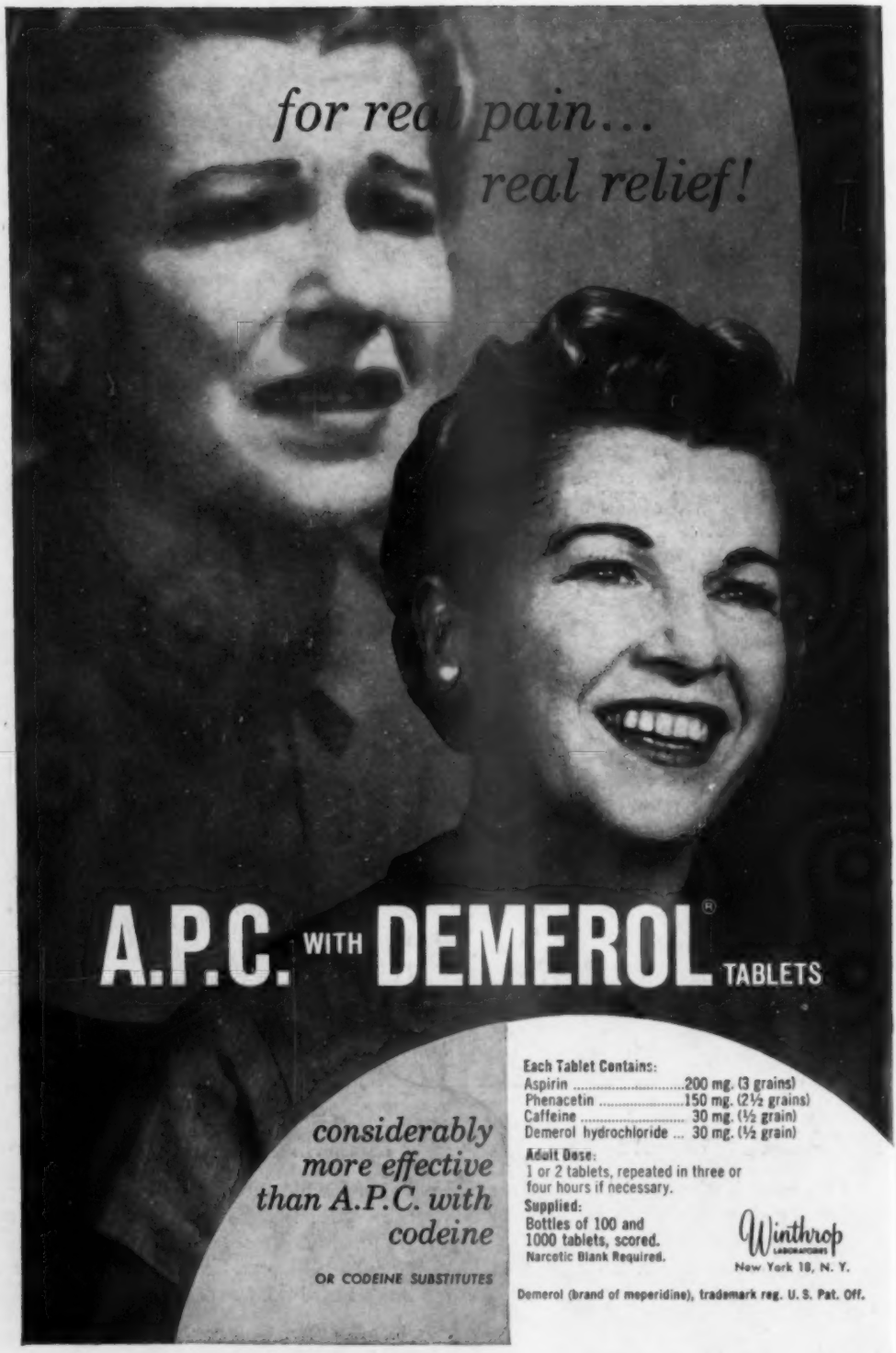
May be chewed, dissolved in mouth, or swallowed with water. Each white, mint-flavored tablet contains glycine 0.18 Gm. and Ca carbonate 0.42 Gm. Bottles of 100 tablets.

## TITRALAC® LIQUID

Relief from a teaspoonful—not ounces or tablespoonfuls. Each 5cc. teaspoonful of white, mint-flavored liquid contains glycine 0.30 Gm. and Ca carbonate 0.70 Gm. Bottles of 8 fluid ounces.

*Patent No. 2429596

Riker Northridge, California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real relief!
A.P.C. WITH DEMEROL® TABLETS
considerably more effective than A.P.C. with codeine
OR CODEINE SUBSTITUTES
Each Tablet Contains:
Aspirin ..... 200 mg. (3 grains)
Phenacetin ..... 150 mg. (2½ grains)
Caffeine ..... 30 mg. (½ grain)
Demerol hydrochloride ... 30 mg. (½ grain)
Adult Dose:
1 or 2 tablets, repeated in three or four hours if necessary.
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Narcotic Blank Required.
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